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ENDOCRINE DIAGNOSTIC CHARTS

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Endocrine Diagnostic Charts

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Henry R. Harrower, M. D.

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A LAND OF PROMISE

". . . the internal secretory glands, which already unfold before the astonished view of the seeing eye, a land of promise beside which the vast territories conquered by Lister and Pasteur are destined to pale into honorable insignificance. . . . They come to us as peaceful conquerors who brook no denial. They lighten our darknesses and show us miracles."—*Prescriber*, April, 1913, vii, p. 89.

INTRODUCTION

"THE DIFFICULTIES of accurate endocrine diagnosis are the prime obstacles to the efficient application of organotherapy." So said a colleague not so long since. It is not such a simple matter, however, largely because the glands of internal secretion have an extremely intimate relation with almost every function of the body, and with one another. The "endocrine diseases," as outlined in the text-books, constitute but a small share of the real endocrine problems which are encountered in every-day practice.

It is easy enough nowadays to find books in which the symptoms of myxedema, Addison's disease, or gigantism, are enumerated, but quite a different matter to differentiate the various shades of endocrine irregularities that may involve only a part of the function of one or more of the endocrine glands.

The complexity of such diagnoses is the greater because of the fundamental importance of the relationship of the endocrine glands. Single-gland manifestations are so uncommon as to be almost rarities. The reason for this is, of course, that, before any functional difficulty localized in a given endocrine gland can exert any influence upon the rest of the body, it must also exert an influence upon the rest of the endocrine glands, for the physiological contacts between the endocrines themselves are almost more numerous than the contacts between the endocrines and the rest of the body. Suffice it to say that endocrine diagnosis is neither simple nor easy, and that the majority of physicians concede that most of their failures in the treatment of endocrine problems are due to faulty diagnosis.

The library of The Harrower Laboratory contains nearly fourteen hundred books on various phases of the internal secretions and more than forty thousand reprints, clippings, and abstracts. Out of all this material, one would think that it ought to be easy to find information regarding anything endocrine, but when I was requested "to condense our present knowledge of endocrine diagnosis into a half-dozen tables" it did not prove to be so easy.

But, as I began to attempt this task, my attention was attracted to a number of tables published in various reprints and books and systems, which appealed to me as worthy of being brought up to date and published here in place of tables that I might work out myself. It is for this reason that some of the following pages are devoted to translations of publications by famous endocrinologists in Europe, and also that the splendid differential chart of pituitary disorders by Engelbach is used as a basis for those found here.

It seemed advisable to give these as they were originally published with the exception of such changes as our newer knowledge has made necessary because, as the reader will see, each of these writers has considered the subject from his own special point of view and has gathered together the data in a very effective fashion which could not very well be improved.

It should be stated here that quite the most effective means of establishing an endocrine diagnosis is *by a successful treatment;* for nothing is more convincing than the change that follows the use of indicated organotherapy. This does not lessen the necessity for a maximum of diagnostic information, and it may be said without hesitation that the most successful organotherapeutists are those who get the most intimate and the broadest conception of what ails the patient, and who, in addition to removing the fundamental factors that cause these difficulties, can build or reestablish the deranged endocrine functions by suitable endocrine encouragement.

In order for these diagnostic data to be of maximum service to the reader, certain fundamentals must be

appreciated. They have been set forth in the preliminary chapters and, unless these basic principles are agreed upon, this little book will fail of reaching its aim—to deliver to the reader information of immediate practical applicability.

After the metal was in page form, it was suggested that the blank spaces at the end of several chapters, might be used to good advantage. So I have taken this opportunity to emphasize some points regarding the technical and business aspects of our work that may be of interest.

Without a question, a number of criticisms and corrections could be made in the material which follows, and these will be welcomed. It is hoped that this little publication may prove of unusual reference value to those into whose hands it may come, and that it may serve to point the way to better endocrine diagnoses and a correspondingly better therapy.

H. R. H.

February, 1929.

I

FUNDAMENTALS OF CLINICAL ENDOCRINOLOGY

Every-Day Endocrine Disorders—Endocrine Active Principles—Functional Endocrine Relations—Different Types of Organotherapy—Hormonic Chemical Regulators —Endocrine Dosage.

THERE SEEMS TO have been more discussion about the internal secretions than any other phase of physiology or medicine.

Thousands of articles have been written on various aspects of the subject, and probably more than 90 per cent. of them have appeared during the last few decades—since the early experiences with thyroid therapy were announced in 1891 by Dr. George Murray, of Newcastle.

In these articles, especially in the discussions and editorial comments, there is the widest difference of opinion ranging from flat contradiction of fundamentals to regret that the facts are not yet entirely clear or that the results upon which the conclusions were based "might have happened anyway." On the other hand, there are many hundreds of articles of the opposite type.

The practising physician who is out to get some useful information that he can apply in his daily work no sooner has decided that a given opinion, which appears to him to be reasonable and to be satisfactorily established by clinical and laboratory experience, is really worth his while, than an editorial comes out loud in its condemnation, or some other article contradicts it.

Almost every original idea in this special field—and they are few and far between—has encountered the most severe criticism, even actual denial. Sometimes the oppo-

sition is not that of the unbeliever, which would be negative in character, but is positive, aggressive, and outspoken. Insinuations are made, innuendos are hurled, and interference comes but little short of propaganda.

The reader is nonplussed. Which facts are fundamental? What may one believe and practise? Who is "an authority"? Who is unbiased and, therefore, able to decide? When is the protracted "infancy" of this subject going to end?

After fifteen years of struggling for the right to hold an opinion and to express it, the writer refers to the record, which is in black and white, and asks the unbiased critic to draw his own conclusions.

Here are six of the much denied essentials that time has vindicated and established. They constitute a series of fundamentals that must be accepted if the reader is to get very far in his study of endocrinology and its application to his work. Doubtless, denials may still be heard in some quarters, but the tumult and the shouting long since have died down. The harsh statements of the critics now lie dormant in their dusty files from which they dislike to have them taken, while the inquirer with his pointed questions asking for explanations is met with evasion—and the subject is changed.

1. Every-Day Endocrine Disorders

The endocrines are of daily importance in the routine practice of medicine.

The physician must consider these glands in all circumstances and in all cases, for they may be involved in all circumstances and in all cases. The crank who "sees glands in every case" is not so foolish after all, for there *are* glands in every case. On the contrary, he who is looking only for the text-book endocrine diseases, such as myxedema, acromegaly, eunuchoidism, or Addison's disease, upon which to test the newly found endocrine measures, is going to be distinctly out of luck.

True endocrine diseases, such as we now expect to find illustrated and discussed in all systems of medicine, are rare. Despite our increasing capacity to spot them, they

do not show up very often even in the experience of the busiest practitioner. This is fortunate if only for the reasons that they are not easy to treat and prognoses usually are very unfavorable. On the other hand, if the reader will realize that the glands of internal secretion constitute a directorate that controls the activities of the body in a very large measure and, in turn, are influenced by the most common factors that bring about disease and death, he will quickly realize how vital their influence is and how important it is to discover as early as possible the slightest irregularities in the production of their chemical regulators.

Pathology is a comparatively hopeless study and, since it represents structural change, is difficult to control, whereas disturbed physiology is functional and something that can be influenced and modified.

A knowledge of the endocrine functions and relations will lead us to an appreciation of the frequency and extent of their disorder in the most common disease-producing conditions like infection, toxemia, and stress. The careful student who has become familiar with the wide-spread ramifications of the endocrine functions and the means of modifying the factors that interfere with them, serves his patients far better than the one who, still seeking for "endocrine diseases" to diagnose and treat, overlooks the simpler functional disturbances of every-day occurrence.

All this brings to the physician in a much more general, routine, practical fashion the possibilities of endocrine therapy in every-day practice; and these possibilities are as innumerable as they are fascinating.

2. Endocrine Active Principles

The endocrine glands produce certain stable and remarkably active substances that can be utilized in therapy to modify either endocrine disturbances or their results.

The epoch-making* discovery of the therapeutic effects of thyroid extract introduced us to a series of procedures

*Will the reader note the adjectives used here? They are all used in the publications of the last few years, chiefly in editorials on endocrine or organotherapeutic subjects in the *Journal of the American Medical Association*, the *Lancet*, and the *British Medical Journal!*

of tremendous import. In fact, it may be said that this event paved the way for this most magnificent and spectacular development in therapeutics. The achievements of the past twenty or thirty years include the discovery of the adrenal medulla principle and its amazing influence in asthma and shock, the separation of the post-pituitary principle and its wonderful effects in labor and upon the intestines in surgery, the perfection of our knowledge of the parathyroids and their decisive control of calcium in the body. The development of insulin, too, which has astounded the world and changed the prognosis of diabetes almost as radically as it is possible to believe, and the more recent perfection of a liver extract so potent in its influence upon blood production that it is capable of doubling and even trebling the red-cell count in some of the most serious types of anemia and pernicious anemia, surely should suffice to give pause to those who criticize organotherapy. These accomplishments are not all that might be listed, for there are others that establish once and for all the incontrovertible position of the organotherapeutist, and that encourage him in his search for still other endocrine products that may be just as marvelous.

Before leaving this matter it should be mentioned that some of the most remarkable possibilities of endocrine therapy have followed the administration of glandular extracts *by mouth.* This has caused a change of heart in those who used to say, "destroyed by digestion, with the exception of thyroid, of course," or "no better than so much ham and eggs; they are all proteins, you know." The fact is, these glandular products have to be digested in order to free the desirable principles and to get them into a form in which they can be assimilated.

These therapeutic possibilities of endocrine preparations, whether given by mouth or parenterally, constitute an essential foundation to the successful study of the principles of endocrinology; and, unless they are accepted, the reader is bound to be deprived of all the good he might get from their utilization in his practice. He is merely marking time at a point in medical research twenty-five or thirty years back!

3. Functional Endocrine Relations

The endocrine glands are intimately related to one another, and conditions that disturb the function of one gland automatically and promptly bring about changes in the others. In other words, we must concede that endocrine disturbances ordinarily are pluriglandular.

This is an extremely important matter about which there has been a greater difference of opinion, it seems, than any other related endocrine subject. As will be seen as the data assembled here are studied, this fundamental principle must be fully understood before the practitioner can attain real success in his endocrine experiences.

It must be remembered that this close relationship of the endocrine glands does not concern just one or two of these organs, although at the present time certain of these relationships seem to be better understood than others. It must be kept in mind that dyscrinism, or disordered function of the endocrine glands, is never a simple, single condition.

For years the pluriglandular idea was considered to be an unscientific, haphazard, "shotgun" theory based on the hope that, if one endocrine product was unsuccessful, two together might do the trick. If, perchance, neither of these was helpful, the addition of a third or a fourth endocrine might reach the cause. This is precisely what happens, and none can deny that three indicated remedies directed at a certain complex are much more likely to reach a larger proportion of the difficulty than one alone. Many customary procedures in therapeutics are based on the same idea. Certainly it is logical that where there is a complex disturbance, complex efforts must be made to combat it.

The experiences of the Great War are a splendid illustration of the fundamentals underlying the successful application of organotherapy—or any other therapy, for that matter. It will be recalled how for several years most expensive and heart-breaking efforts were made to attain certain objectives, first in one part of the line, then in another. The success in one place was neutralized by failure in another, and so this unfortunate martial give-

and-take continued for years. Then, suddenly, as though the idea had just dawned, it was decided to correlate all activities and to attack all the sectors together. The result was success.

Surely, this principle applies in the great fight against disease. It stands to reason that, if pluriglandular disturbances are a reality (and we know they are), then our attack upon one endocrine sector alone is going to leave the others virtually uncontrolled. To make one attack after another, first on one sector and then on another, may be entirely scientific, as the proponents of this method insist, but it does not give the desired results. An example of this procedure is the treatment of obesity in which thyroid is given for a few months, then pituitary for another few months, and perhaps later even a course of ovary for a time. The patient naturally is more interested in being benefited than in assisting her physician to attain accurate information regarding the condition of the individual glands in question. When we are carrying on an endocrine battle involving many sectors, we must treat all of them together thus fighting a concerted, comprehensive battle.

The menopause gives us a peculiarly apt illustration of this principle. Here we have a normal, natural, and expected ovarian endocrine insufficiency. If the problems of this particular period were of an ovarian character pure and simple, the change of life would be simply the cessation of ovarian function and reproductive capacity—and that would be all. Unfortunately, certain of the other most intimately related endocrine glands seem to manifest unusual concern at the waning ovarian activity. This is shown first by a compensatory functional reaction, later perhaps by some structural changes in the most closely related glands (the thyroid and the pituitary), and still later in many cases by the exhaustion of their functional capacity. These compensatory reactions are undoubtedly the cause of many of the sympathetic nervous and circulatory manifestations that constitute the symptom-complex of the climacteric. Instead of a simple *normal* hypo-ovarism we have a distinctly *abnormal* condition on the

part of several of the glands, notably the thyroid, pituitary, and adrenals.

Ovarian therapy is known to be effective in certain menopausal cases. It is helpful because it mitigates the extent of the ovarian insufficiency, thereby lessening the demand upon the thyroid or the pituitary that already may be overburdened from other causes. If, however, as is the case in so many individuals, the problem is decidedly triglandular and involves both the pituitary and the thyroid with the ovaries, how can treatment directed at the single ovarian phase be other than indirectly beneficial to the equally important, or perhaps more important, thyroid and pituitary factors?

Uniglandular therapy of this triglandular disorder may be compared to the battle referred to above or, to use a physiological illustration, to a digestive difficulty involving the stomach, small intestines, and colon. Treatment of such a condition by a single measure directed at the difficulty in only one of the affected parts will certainly fail, whereas a treatment that is directed at conditions in all three places at the same time will be far more likely to bring results.

I have never been able to see why the combination of endocrine products should be so wrong when the very persons who are loudest in their condemnation of such comprehensive measures are those who are in the habit of using combinations of other measures or remedies. In fact, as I see it, it is very much more reasonable to attempt to supplement certain known endocrine deficiencies that accompany one another than it is to combine iron, quinine, and strychnine, or aloin, belladonna, and strychnine, because we happen to know that each exerts a certain complementary influence that fits in with that of the other. Organotherapy involves the replacement of certain vital substances that are lacking or missing in the body. To supply one of these at a time, or to fail to supply more than one when the others are just as vital and necessary, seems to me to be the height of therapeutic folly, even though so often it has been called "most empirical and altogether unscientific."

4. Different Types of Organotherapy

The two main types of organotherapy are often confused and misunderstood because they are so fundamentally different in character. These are: Substitutional, or homostimulative, and pharmacodynamic. The former is active through its influence upon the body, especially the endocrine glands that correspond to those from which the remedy is obtained, and also through its hormone* capacity to reestablish the slowed endocrine activity. The latter type, on the other hand, has a more immediate and direct influence, strictly drug-like in character, lasting but a short time, and is not necessarily related to the function of the gland from which the extract is prepared. It is extremely important to keep this difference in mind, for criticism has come from confusing these two essentials.

A few illustrations may be recalled here to emphasize this point and to help the reader to avoid drawing similar unfortunate and erroneous conclusions. Already eight or ten very active, standardized endocrine principles have been separated and perfected. Their influence in the laboratory, and in the clinic as well, is astounding. These endocrine principles are being used in medicine with the highest satisfaction, and their pharmacodynamic effects may be employed to the greatest advantage. For example, insulin is capable of facilitating the metabolism of carbohydrates in a direct and spectacular fashion. It does so regardless of the condition of the pancreas in the animal or person to whom it is given. Insulin will cause hypoglycemia in normal persons as well as in diabetics. The fact that insulin controls hyperglycemia in pancreatectomized dogs shows that its influence is not brought about through the pancreas, and is confirmation of this. Yet, there are still those who express themselves as to the futility of any form of pancreas therapy other than the endless injections of insulin, because it is easy to prove that it does not cause the same rapid and measurable physiologic effects. Pancreas therapy, however, certainly

*The word *hormone*, from the Greek, I arouse or set in motion, was coined to indicate the stimulating character of the internal secretions. Undoubtedly they act as catalytic agents.

may exert a homostimulative or catalytic influence upon pancreatic function. Scores of articles and perhaps tens of thousands of experiences confirm this statement. But this homostimulative effect is gradual, comparatively slow, and entirely dependent upon the responsiveness of the pancreas which we are trying to bring back to more normal activity; whereas insulin reduces an abnormal blood sugar in twenty minutes, even though its immediate effect lasts only for four or five hours. The possibilities of restoring pancreas function in the same fundamental manner in which we have come to expect other endocrine products to work, have been largely overlooked because of the brilliance of the insulin discovery.*

As well might we expect to explain the influence of the post-pituitary active principle in labor on the basis of a temporary hypopituitarism, or asthma as a hypoepinephrinemia (adrenal medulla insufficiency) because epinephrine so often is amazingly effective in this disorder. It would be ridiculous to expect pituitary substance to act as a pharmacodynamic remedy like Liquor Pituitarii, or *vice versa.* It would be equally absurd to try to regulate an endocrine irregularity, such as hypothyroidism, in the same rapid and spectacular manner that one can control intestinal paresis with the post-pituitary principle, or a paroxysm of asthma with epinephrine. We cannot judge an essentially homostimulative remedy by its pharmacodynamic action.

Let us recapitulate for a moment: There are two great types of organotherapeutic remedies—the catalytic or hormonic, and the pharmacodynamic. The former replaces something that is missing, which again arouses or sets in motion certain functions through an essential or hormonic catalytic influence; the latter exerts a direct and drug-like influence of a specific nature. The former has many

*In passing, it may be of interest to mention a report of research work performed at the University of Toronto. Dogs from which the pancreas was successfully removed were given sufficient insulin to maintain the blood sugar at a normal level, yet the subnormal weight, polyphagia, and polydipsia were not controlled. Upon the addition of pancreas by mouth, they were kept in a perfect condition of nutrition. (*Jour. Am. Med. Assn.*, April 11, 1925, lxxxiv, p. 1122.)

more organotherapeutic possibilities because its principal aim is to supply what is lacking in the organism and to help to reestablish the waning endocrine function and thus set the body to work again at its regular job and at the proper speed. The latter is said by some to be more scientific—probably because many of the endocrine principles are now capable of standardization. Whether it is more scientific or not, we must admit the difference between these two fundamental forms of organotherapy and thus avoid falling into the serious errors that a misunderstanding of them has brought about.

5. Hormonic Chemical Regulators

The hormones are definite chemical substances of remarkable activity, several of which already are isolated and even capable of synthesis. Most of them are quite stable, that is, not destroyed by digestion in the stomach, intestines, or blood, and are notably resistant to heat. They are normally taken up by the cells that they are expected to influence.

It has been shown by many, many workers that this chemical regulation of certain functions of the body can be carried out artificially under the abnormal conditions that are brought about in the laboratory or that occur in sick persons. However, the fact that such a mass of work has been accomplished in the laboratory has led to a state of affairs which, I believe, has blinded the eyes of many a well-intending student. For instance, is there any comparison between an animal that has been pancreatectomized and a patient with the pancreatic insufficiency of diabetes? Both are suffering from a lack of certain substances and both benefit by the administration of these substances; but the combination of circumstances that has resulted in diabetes in the patient surely cannot be compared in origin, rapidity of development, or complexity, with the surgical diabetes produced in the laboratory. This being the case, the experience in the laboratory in the treatment of artificial diabetes is not comparable with that expected in practice. The physician

must think in terms of patients and disease, not in terms of dogs and experiments.

When the demand for exact observation is made and approved, this does not mean that such a thing is impossible outside the physiological laboratory—if we admit that it is possible there. It must be granted that in living organisms (humans and animals, even plants) rules have but relative value, and the investigator is constrained to do the best he can. For that reason, absolute laws or rules are dangerous and prone to lead one astray.

The point that I want to make is this: Clinical experience has shown a number of glandular substances to give good service in certain forms of disease. They are used successfully singly, but, many times, much greater success results from their combination with others. *That* glandular therapy is of use, has been proved many times. *Why* glandular therapy is of use, is not for the practitioner but the physiologist to find out. In the meantime, the practitioner will go on in his empirical way because it is rational, and he will give his patients the benefit of his experience. That is not only his privilege; it is his duty. If it be unscientific, he must still make the most of it.

I well recall a visit with a prominent physiologist who has been very harsh in his denunciation of the "unscientific" conclusions that have been made in clinical endocrinology. In a discussion of ovarian therapy, to which this gentleman was thoroughly opposed, he used the thyroid gland as an illustration of a *real* endocrine gland and, in substance, said this: "We take a small animal and remove the thyroid, and, if we start early enough, we can entirely replace the missing thyroid by feeding the gland, injecting thyroxin, making transplants, or by combinations of these. Every influence that the thyroid is expected to exert can be substituted, and the animal will grow, develop, reproduce, and be as though its thyroid had never been removed." This is all very true and applies to the parathyroids, the pancreas, and perhaps to other glands as well. However, the point that I wish to make refers to the provisional clause, "if we start early enough." When I asked why this was added, there was a long pause, which

I finally broke by remarking, "If you do not start early enough, you cannot accomplish the desired results by thyroid alone, for from the moment that gland is removed every other endocrine mechanism in the body begins a vigorous attempt to replace its action and to lessen the serious results of its loss. Every minute that passes between the time of operation and the initiation of treatment, makes for a more complex, more difficult, *and more pluriglandular problem.*"

It must be remembered that no patient comes to a physician in practice with so sudden and complete an endocrine irregularity as that inflicted upon the animal whose thyroid is removed. As we already have seen, the longer an endocrine defect is allowed to continue, the more complex and pluriglandular it becomes.

6. Endocrine Dosage

The principles underlying the dosage of endocrine substances differ from those involved in drug therapy.

Our attempts to treat endocrine irregularities by hormone therapy are about as physiological as any method could be—we are replacing something that is missing and, coincidentally, we are encouraging the body to produce more of this missing substance (presumably by catalysis). This is very different from the administration of drugs, which are given for their pharmacodynamic influence and not to replace something that is lacking. This great difference, already discussed, has everything to do with the fundamentals of organotherapeutic dosage as well as with the availability and activity of endocrine principles used in therapeutics. Morphine exerts a certain, definite, sedative effect that usually is in proportion to the dose given and the weight of the patient. The patient in need of morphine is not suffering from a lack of morphine, but from conditions that this drug is capable of modifying. The same is true of strychnine or any other drug, including the pharmacodynamic endocrine principles already referred to. This is not true of the thyroid principle when it is used in hypothyroidism, or of the parathyroid principle in the case of tetany, or of the ovarian principle in

the case of infantilism or sterility. Here we accomplish something that the body has failed to perform. This is made possible by knowledge that we can use the physiological activity of an animal in building up a certain substitution very similar to, if not identical with, that missing in the patient; we simply transfer it from the one to the other.

A physiological law or fundamental was set forth years ago by my friend, Dr. L. Hallion, of Paris. This has come to be known as "Hallion's Law" and is as follows: "Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration." Such a principle explains many experiences with organotherapy, for times without number physicians have noted a far greater benefit from an endocrine remedy than could possibly be attributed to the comparatively small dose given. The real benefit came from additional service that the lagging gland itself was encouraged to perform. The advantage, then, is really due to the reaction to the remedy rather than to its direct influence—a very different thing from a pharmacodynamic effect.

What is the proper dose of an endocrine principle when given for its homostimulative action? This question has been asked a thousand times, but there is no really satisfactory way of evaluating endocrine insufficiencies and of knowing what the body needs or can appropriate. For explanations of what undoubtedly happens, we have to resort to a theory that I crystallized twelve or fifteen years ago under the alliterative phrase, "an hypothesis of hormone hunger." (*Med. Rec.*, Aug. 16, 1919, xcvi, p. 276.) This explanation seems to elucidate satisfactorily to some, but not to others. I called it an hypothesis, so I suppose it is just as difficult to disprove it as it is to prove it. Suffice it to say that I conceive the blood to be the stream in which all the endocrine principles, ferments, nutritive elements, and, of course, the cells and other solid elements are flowing from one part of the organism to

another. For instance, the blood reaches the ovaries with certain substances in it that are of special interest or usefulness to those organs—notably the thyroid principle and the anterior pituitary principle. Undoubtedly there is a certain cellular capacity that enables the ovarian cells to "grab" the needed substances that are streaming by. This, however, is not a theory but a fundamental principle known as "cell selectivity" which applies in many other chemico-cellular circumstances than those involving hormone influences. The hypothesis comes in by my suggestion that in certain circumstances, for example, where there is a reduction in the production of the thyroid hormone, there is a corresponding lack, or want, or hunger, on the part of the ovarian cells for this substance, and *this "hunger" must vary with the needs of the ovaries for this substance and the capacity of the thyroid to supply it.* Obviously, then, when we come along with our organotherapy and begin to replace some of this missing substance, just as the thyroid is stimulated by thyroid therapy and avails itself of our proffered assistance, so the ovarian cells grab *with a greater avidity* the substance that they require most.*

At all events, this gives us a fairly satisfactory explanation of how various parts of the body can avail themselves of what they need *in proportion to their needs* and, I suppose, how certain substances that are not needed are rejected and allowed to remain in the blood until used elsewhere or oxidized.

These six fundamentals are prerequisite to the practical application of the knowledge now available in endocrinology. It is a source of great gratification to be able to compare the present attitude of the profession to these very ideas with that held only five or ten years ago and to see how thoroughly they are coming to be admitted and appreciated.

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*The principal opposition to this hypothesis has been based on the fact that, if we administer thyroid extract in overdoses, the cells may take it up and be detrimentally influenced thereby. But thyroid extract *in excess*, like any food, drug, or poison *in excess*, is a very different thing from thyroid within normal limits. And, of course, I had in mind the *intelligent* administration of the remedy!

II

THE CAUSES OF ENDOCRINE DISORDERS

Heredity—Environment—Emotional Stress—Toxemia and Detoxication—Allergy, Hypersensitiveness, Idiosyncrasy—Drugs and Drug Addiction—Other Dyscrinisms—Cancer, Tumors, Etc.—Senility, Old Age.

IN THE PRACTICE of medicine, success comes largely from the appreciation of causes rather than effects, and from the broader treatment that such added knowledge makes possible. It is just as wrong to treat endocrine symptoms and ignore their origin as it is to treat any disease symptomatically alone.

The successful endocrinologist is the one who can uncover the reasons for the difficulties submitted to him, and who, while he is attempting to modify the dyscrinism and its immediate effects, naturally is making every effort to control the causes. Organotherapy very often fails in proportion to the extent of our view-points!

Heredity

Some endocrinopathic individuals are born that way; others become so. It may safely be said that the majority of the latter have a constitutional vulnerability in that direction so that there is at least a potential hereditary feature.

The causes of endocrine disorders are either congenital or acquired. Hereditary factors are paramount among the congenital causes, and it is probable that the constitutional causes must be included under the hereditary factors. The constitution with which we

are born is really inherited, since it is transmitted to us by our progenitors. The congenital endocrinopathies, however, are those troubles that are acquired by the fetus in utero because of some illness that affects the mother.

Among hereditary endocrinopathies, especially may be mentioned extreme hypothyroid conditions, such as myxedema and cretinism, which are notoriously "familial" afflictions. Cretinism tends to recur in a family, even in a locality where only a fraction of the community is affected. This leads to the conclusion that the constitutional hereditary factors play a part in determining the insufficiency of the thyroid gland in the presence of unfavorable environmental conditions. The cretin is such not merely because of an abnormal thyroid but also because of abnormal chromosomes that determine such an abnormal or peculiar thyroid—a thyroid that functions inadequately only when the environmental conditions are not at their best; in other words, a thyroid that is constitutionally sensitive to variations in the environment.

It is fairly generally conceded that endocrine dissimilarities account quite largely for racial differences in both traits and appearance—a factor that is instanced by the subthyroid facies of the Mongolian and the hyperadrenal activity of the Caucasian. In diabetes mellitus, which is among the endocrine diseases that are considered to be hereditary, not only is there a likelihood of a familial predisposition but even a racial predilection; *e.g.*, Jews are peculiarly prone to develop the disease. This special liability, however, probably depends as much on their worrying, nervous disposition, and their liking for rich and sweet foods, as on any special frequency of a diabetic diathesis proper.

Any anomaly that the growing fetus in utero acquires because of unfavorable conditions (for instance, diseases affecting the pregnant woman), is congenital though not necessarily transmitted by heredity. These particular conditions, therefore, stand between the congenital (in the strict sense of the word) and the acquired

endocrine disorders. They may be induced by severe infectious diseases suffered by the mother, such as smallpox, diphtheria, scarlet fever, etc., or they may be due especially to syphilis and other serious diseases. Goiter, or the tendency to it, undoubtedly is transmissible through the mother. Hypothyroidism in the pregnant should be treated and forestalled where possible, if only for the advantage such treatment will be to the unborn child.

Then there are certain toxic conditions—such as those that may induce pernicious vomiting and other forms of toxemia—which are prone to leave an impress upon the growing fetus. Undoubtedly, factors that cause dyscrinism in the mother are influencing the endocrines of the child in identically the same way. Diabetes mellitus in pregnant women must affect the children, though fortunately it is rare, because well-developed diabetes in women is prone to cause sterility. Whether diabetes as such is transmitted by heredity or not, it may be assumed that the functional ability of the infant's pancreas is at least impaired.

Deprivation as suffered during the War, especially in the central European countries, affected the children, who were born constitutionally deficient and relatively non-resistant to pathogenic factors. Many had an "endocrinopathic inheritance" thrust upon them which is only beginning to show itself now. It is a fortunate compensation that extreme deprivation and want often induce sterility by suppressing ovulation, otherwise even more war babies would have been born to increase the host of misfits. During famines and pandemics, the infants that manage to be born at term (there are many abortions and miscarriages) are defective in many ways.

Environment

During infancy and childhood, during adolescence and adult life, environment is an important etiologic element. Conditions of unsatisfactory housing (basements, tenements, crowded conditions, dampness, absence of light, etc.) tend to cause a stunted, incomplete

development of the small child. Such factors influence the endocrines also, and the resultant dyscrinism makes bad worse.

The matter of diet is important too; and deprivation of food, or food deficient not only in its caloric content but in the essential food factors, will injure the endocrine system. This is particularly true of the vitamins, which many are beginning to believe are active largely through the endocrine glands.

Geographic and climatic conditions undoubtedly are factors. It is an interesting observation, for instance, that young and middle-aged women moving to Southern California become stout more readily than they do in their former homes. We know of one case that is virtually an experiment: A young woman, a nurse, who in her home in Oregon is moderately plump, is in good health, and menstruates regularly. As soon as she comes to Southern California, amenorrhea develops, she becomes heavier, her mentality is dulled, and she seems to be not only markedly hypo-ovarian but also hypothyroid and hypopituitary. She has gone back and forth repeatedly—always with the same result.* However, there is another phase of this which is of far more importance: Caucasians who live in tropical countries seem to suffer with regard to their adrenals, which are apparently overstrained—for example, the syndrome of hypoadrenia is uncommonly frequent among Europeans in India. As yet it is not known whether cases of thyroid upset and diabetes mellitus are more numerous in tropical countries, but some day more data will be available. It seems that diseases associated with insufficient hepatic functioning—of both the external and the internal hepatic secretions—are accentuated in hot climates.

Undoubtedly a different influence is exerted upon the endocrines by a strict vegetarian diet on the one hand, and a mixed or a largely meat diet on the other. A

*It is suggested that this interesting coincidence should be deleted for it might militate against our growth and progress here in sunny California. I leave it in!

very important factor is the completeness of the supply of the accessory food substances—the vitamins and the mineral salts—as may be seen in patients afflicted with deficiency diseases in whom some of the endocrines are gravely depleted. The effectiveness of the digestive and assimilative apparatus enters here, but this point will be considered under the heading of toxemia of endogenous origin.

Emotional Stress

Mental or emotional stress is a potent cause of endocrine trouble. The classical investigations of Walter B. Cannon on the influence of pain, fear, and rage have shown the effects of emotional upset on the endocrine functions. ("Bodily Changes in Pain, Hunger, Fear, and Rage," D. Appleton & Co., New York, 1915.) Then there is the unfavorable influence of worry, of shock, of apprehension, all of which are endocrine depletants, especially if continued for a long time. The fatigue-syndrome, which Edward Ochsner described vividly a few years ago ("Chronic Fatigue Intoxication," G. E. Stechert & Co., New York, 1923) and which is one phase of what has been called "shell-shock,"* is a condition of depleted emotional equilibrium in which the endocrines are decidedly concerned. We are familiar with the "nervous breakdown" suffered by people exposed to sudden fright, apprehension, and stress in general, such as, for instance, the Iroquois fire in Chicago, many of the survivors of which have been neurasthenics ever since. Survivors of calamities like destructive fires, earthquakes, floods, shipwrecks, and so forth, always will show the results of fear, shock, and mental and emotional stress in general. The impress is upon the thyro-adrenal mechanism and, through it, on various other functions and organs. Exophthalmic goiter has been caused many times by fright alone.

*Incidentally the writer was among the first to emphasize the essentially adrenal character of shell-shock and war neuroses. (See "Shell-Shock and the Internal Secretions with Suggestions as to Treatment," *Prescriber*, Oct., 1916, x, p. 203.)

Toxemia and Detoxication

Toxic conditions of all sorts exert a strain on the endocrines, more especially on the detoxicating glands, namely, the liver, thyroid, parathyroids, and adrenals. They are the outstanding causes of dyscrinism. Toxemia may be of either endogenous or exogenous origin. The endogenous toxins originate in defective cell chemistry or in alimentary poisons, or they may be due to the gradual absorption of the bacterial protein products from foci of infection anywhere in the body. The consideration of such foci forms a connecting link with that of the exogenous toxins, because infectious foci may be produced by bacteria coming from without as well as by those bacteria that commonly exist within the body. One cannot say that they exist there "normally," but they always exist there "naturally"; for instance, the bacteria present in the colon are facultatively pathogenic. Very potent sources of toxic strain on the endocrine glands are presented by infectious foci in tonsils and lymph nodes, in the appendix, in the ovaries and tubes in women, in the urethra and prostate in men, and elsewhere. The constant absorption of toxin from these foci entails a continued demand on the resources of the detoxicating endocrine glands, which in course of time may lead to exhaustion and then to a great many symptoms which may express themselves generally or locally.

Toxic material having its origin in an incomplete disintegration of food substances, especially proteins, is a frequent source of strain on those endocrine glands that have to do with detoxication. It has been said that detoxication by the liver is exerted particularly against the toxic products brought from the intestine through the portal vein. The detoxicating influence of the thyroid is directed more particularly against the poisons produced by bacteria that have invaded the body and against those substances that may have passed the liver barrier. The detoxicating action of the parathyroids is directed chiefly against the wastes, acid in nature,

which these little glands are capable of modifying through their spectacular regulation of the body's store of calcium.

The demands on these detoxicating organs commonly become so excessive as to break down their functioning ability. For instance, when excessive demands have been made on the liver for the production of the detoxicative hormone, which normally causes the disintegration of toxic products of incomplete protein cleavage, functional hypertension may result and, under certain conditions, hypotension may develop, either because of exhaustion of the pressor organs or because of initial constitutional peculiarities. This functional hypertension is thus closely associated with a depletion of one of the hepatic endocrine functions, which explains the efficacy of Anabolin in such cases. (See page 129.) Similarly, extreme or unduly continued demands on the detoxicating resources of the thyroid or parathyroids, may cause these organs to become exhausted, with the development of certain typical clinical pictures, which are discussed elsewhere.

Exogenous toxins are produced in the course of infectious diseases and exert a most severe strain on the endocrine glands. The most spectacular instance is the depletion of the adrenal glands produced by the bacteria of influenza. This is responsible for the prostration characteristic of the disease; it also explains the protracted and slow convalescence, the tendency to relapse, and other peculiarities, especially the circulatory picture. The clinical results which follow the application of adrenal support in such cases, are confirmation of our conclusions. (See page 86.)

It is known also that changes arise in the pituitary body during acute infections, and hypercolloidism has been found in this gland following experiences of this nature. Pituitary obesity has commenced after an attack of scarlet fever in early childhood, and frequently one can trace major signs of hypopituitarism to acute infections, infectious diseases, or poisoning of some kind or other.

Allergy, Hypersensitiveness, Idiosyncrasy

An interesting cause of stress to which certain endocrine glands may be subjected is presented by certain allergic reactions which are due to a condition of hypersensitiveness, and which may become responsible for idiosyncrasies with regard to certain food substances. There is hypersensitiveness to protein substances only, in which the sensitizing factor may originate within the body, or at least within the intestinal tract which, strictly speaking, is not within the body. With regard to this, W. W. Duke ("Allergy: Asthma, Hay-Fever, Urticaria, and Allied Manifestations of Reaction," C. V. Mosby Company, St. Louis, 1925, p. 138) says: "One frequently wonders whether or not certain individuals become sensitive to substances originating in the body proper. Substances absorbed from the alimentary tract are in reality exogenous in origin since the alimentary tract is nothing more than a tube passing through the body, and substances contained in it are outside the body in the same sense that substances are outside the body proper when in contact with the mucous membrane of the mouth or the skin. One would not believe it likely that individuals could become sensitive to and react to substances of endogenous origin which are present constantly in bulk. Substances of this nature should either cause death or give rise to tolerance so that in the course of time patients should cease reacting to them. However, conditions frequently arise that make one suspect sensitiveness to a body substance which is produced or distributed only under unusual circumstances. This view, however, is difficult to prove. In one case observed by the writer, severe manifestations of allergy appeared each month just prior to menstruation. The attacks were associated with dysmenorrhea, and ceased immediately when the flow from the uterus was established. In three cases, patients suffered a severe attack of allergy coincidentally with the weaning of a baby. The attacks could be relieved by the free use of a breast-pump."

The rôle played by the organs of internal secretion in

the symptomatology of reactions of hypersensitiveness, is illustrated by Dr. Duke as follows (*loc. cit.*, p. 145): "This should seem self-evident when we bear in mind that the great majority of cases, regardless of their severity, can be completely relieved through the action of adrenalin. Many cases can be relieved by pituitary extract. If adrenalin has a normal physiologic antagonist (and one might easily believe that this is the case) an overproduction in this might, on theoretical grounds, give rise to a reaction. Thyroid extract in occasional cases is beneficial, especially in patients whose metabolism is below par and whose temperature runs markedly subnormal. The above influences from a practical view-point, are effective in many cases, but would seem usually to be secondary factors in the etiology of reaction."

Suffice it to say that the study of protein sensitization is a very intriguing one to the endocrinologist, not only because the difficulty may have something to do with irregularities present in certain endocrine detoxicating functions, but because these special protein toxemias undoubtedly are capable of interposing a subtle interference to normal endocrine physiology* which indeed may be the chief etiologic factor in a given problem case.

Drugs and Drug Addiction

It is a natural assumption that the endocrine glands are influenced by drugs, the effect of which may be either beneficial or detrimental. So far as is known, the first study in this respect was reported by my good friend, Dr. C. E. de M. Sajous, of Philadelphia ("The Internal Secretions and the Principles of Medicine," Volume II, 1908, Chapters 18 to 22), who enumerates and describes drugs that enhance the defensive proper-

*I am convinced that the majority of cases of vomiting and nausea of pregnancy are a form of protein sensitization—to products of the new organ, the placenta. This seems to have been proved conclusively by the successful use, for more than ten years, of a form of organotherapy known as Placenta Co. (Harrower)—see page 107—and more recently by my Placenta Protein Sensitization Test (*Clin. Med. and Surg.*, April, 1927, xxxiv, p. 279).

ties of the blood by promoting the formation of auto-antitoxin and incite an artificial fever by exciting the vasomotor and sympathetic centers; remedies that depress the functions of the adrenal, vasomotor, and sympathetic centers. Many of these drugs will, in suitable doses, promote and encourage the functioning of the endocrine glands. Any harmful effect necessarily is dependent on doses larger than required and sufficient to overtax the ability of the glands to respond. Some of these drugs, *e.g.*, strychnine, undoubtedly can act as do the intestinal poisons, by causing overexertion of the endocrine functions, which at first induce excessive functioning and then depletion.

There are certain drugs, however, that almost invariably exert pernicious effects, at least when taken habitually and in large doses. It has been observed clinically that alcohol, coffee, and tobacco, prevent the beneficial action of adrenal therapy. The conclusion is justified that, if taken in excess, they will depress adrenal functioning; and this is borne out by Sajous and many others. The same result follows the habitual use of narcotics and even of the non-narcotic sedatives. This is the reason why drug addicts usually show such marked muscular atonia and such very low blood-pressure readings. Parenthetically, it may be added here that there are real possibilities for the support of the depleted adrenals (with Adreno-Spermin Co.—Harrower) during the stormy withdrawal period in the treatment of drug addicts.

Other Dyscrinisms

It is a common observation, and an undoubted physiological fact, that any disturbance of the endocrine equilibrium will produce consequences. If, for instance, one endocrine organ is diseased and its activity impaired, or if it is removed, its synergistic endocrine glands will be induced to overact; and its antagonists, being no longer checked or restrained, will also tend to function to excess. As we have already seen, the best-known instance of this kind is the gradual or abrupt elimina-

tion of the ovarian internal secretions from the organism either during the change of life or by operation. It is a common observation that those two glands that are intimately associated with the ovaries, namely, the pituitary and the thyroid, are incited to unusual exertion which sometimes is so great as to bring about exhaustion. This may explain the symptoms of pluriglandular defect which so frequently develop in relation to the menopause, the best known of which are climacteric obesity and climacteric myxedema. It is well known that removal of the ovaries in women may be followed by permanent hyperplasia of the pituitary body.

Disease, especially tumor of the adrenal cortex, may whip up the gonads to precocious development in children or it may change the feminine peculiarities in women to masculine traits (virilism, hirsutism). Pineal tumor has also been claimed by some writers to be responsible for precocious puberty in small children, especially boys.

Another instance of an influence on certain endocrine organs, through the elimination of others, is the fact that, physiologically, the thymus commences its involution in infancy and is supposed to complete it at the fifth or seventh year, thereby removing its check on the development of the genital organs. If the thymus persists instead of undergoing its physiological involution and if in consequence the gonadal development is delayed and impaired, abnormal development of the total organism results. The so-called "thymocentric" individuals are never normal.

Processes that are of themselves physiological, also may become responsible for glandular changes. An interesting instance comes to mind: In pregnancy the anterior portion of the pituitary usually shows a multiplication of large neutrophilic elements (S. W. Bandler, "The Endocrines," p. 110) which apparently are derived from the normal cells. After delivery, the gland involutes but, it is claimed, never goes back to its previous size. This change, occurring in successive pregnancies,

may bring about a physiological inactive condition of the gland and may produce the adiposity, loss of hair, asthenia, and subnormal temperature often seen in women who have had many pregnancies. On the other hand, overactivity may persist, leading first to acromegalic changes with final insufficiency.

The interstitial cells of the genital glands (Leydig cells) and the cells of the corpora lutea exercise an important rôle in interglandular relations and, therefore, in the derangement of these relations.

Cancer, Tumors, etc.

Endocrine glands are subject to malignant disease as are all other tissues of the body. Even when the glands are not actually the subject of malignancy their functioning is necessarily impaired by the devitalizing results of malignant disease elsewhere in the body, especially by the resulting cachexia. Addison's disease, a classic adrenal picture, is certainly a tumor whether it is due to tuberculosis, as most of us believe, or to cancer. The effects of tumor in the adrenal cortex and in the pineal have already been mentioned. Tumor formation in the hypophysis may be malignant or benign, but it causes many essentially pituitary symptoms as well as the so-called "neighborhood" pressure symptoms outlined fully on page 43.

Senility, or Old Age

Dr. A. Lorand and many other writers call old age a "disease." Serge Voronoff, whose studies are epoch-making even if his methods may not be so well appreciated, describes the process of becoming old as being due to a gradual increase of the connective-tissue cells which replace the "noble" tissue cells, preventing their regeneration. This unphysiological increase of connective-tissue cells impairs the vitality and functioning ability of all endocrine glands as it does with relation to other organs. It lessens the production of internal secretions and is, thereby, responsible for the waning strength and

energy, both physical and mental, and the growing fatigability of the organism so characteristic of old age. The metabolic processes are gradually slowed down; in short, the organism becomes old. Senility is characterized by increasing deficiency in all endocrine functions. Presenility, resembling senility in all respects save the age incidence, is essentially a manifestation of endocrine depletion—hypocrinism.

Harrower Policy

A CONDENSED statement of the Harrower policy may be expressed thus: *Semper melius fiat.* ("Let it always be better," or "always improving.") This splendid slogan was suggested by a colleague who noted a recent minor change in one of our formulas. As a matter of fact, we had just succeeded in concentrating Sol. Placento-Luteum Co. (Harrower) to make it contain 4 per cent. instead of 3 per cent. of the combined nucleoproteins of the corpora lutea of pregnancy and the placental parenchyma—an increase of 33 1/3 per cent. in its therapeutic usefulness. (See page 88.) This solution, which is used in certain cases of vomiting of pregnancy (about 30 per cent. of the total number encountered), is appreciated by many physicians for its superiority over solutions of corpus luteum alone. The product is now that much better.

It is a regular policy of the house always to make a change, regardless of cost, if it is seen to be of decided advantage to the physician or to the patient. For instance, a few months ago a well-established and appreciated product, Folliculin, was dropped from our list, despite the fact that it was the first of its kind to be made available to the profession in this country. The reason is that we now offer in its place an apparently identical, standardized product called Plestrin, *which has five times the potency at one-seventh the previous unit price.*

Some time ago a vital change was made in the formula, Hepato-Splenic Co. (Harrower), by adding two hepatic detoxicative stimulants—Anabolin and boldine—to the older formula, thus increasing its value as a means of accelerating hepatic detoxication. Anabolin did not exist when Hepato-Splenic Co. (Harrower) was first formulated. As with the more recent change in Sol. Placento-Luteum Co. (Harrower), so with the improved Hepato-Splenic Co., there was no increase in price. So there is always something to be striving for—always to be improving. *Semper melius fiat!*

Character	*Organ*	*Product*	*Role*	*Relations*	*Diseases*
A. NUTRITIONAL AND TROPHIC SUBSTANCES 1. Substances Assisting Nutrition	(a) Adrenals (Medulla)	Epinephrine	Sugar Mobilization Sympathetic Stim.	Adrenals, Pancreas Liver	Hyperadrenia, Addison's Disease
	(b) Liver	Glycogen Hemopoietin	Energy (muscular) Hemopoiesis	Liver, Muscles Liver, B. Medulla	Hepatic Diabetes (?) Anemia (esp. Pernicious)
	(c) Pancreas	Insulin Trypsin	Glycolysis CH. utilization Digestion	Pancreas, Adrenals, Liver, Pancreas, Duodenum	Diabetes Mellitus, Pancreatitis, Indigestion, etc.
2. Detoxicative Regulators	(a) Liver	Anabolin	Detoxication Ureagenesis	Liver, Parathyroids Thyroid	Hypertoxemia (defective hepatic detox.) Hypertension (functional)
	(b) Parathyroids	Parathyrin	Detoxication Calcium Fixation	Parathyroids, Liver, Thyroid	Hypocalcemia, Tetany, Hemophilia, etc.
	(c) Thyroid	Thyroxin	Regulation of Metabolism	Thyroid, Parathyroids, Liver	Hypothyroidism, Cellular Infiltration. Obesity, Hyperthyroidism
3. Morphogenic Stimulants	(a) Gonads (M) (Leydig Cells)	Lydin	Development SecondarySexChar.	Testes, Thyroid, Pituitary, Thymus	Infantilism, Eunuchoidism, Asexualism, Aspermia
	(b) Gonads (F) (Ovaries, C. Lutea)	Lutein Folliculin	Reproduction	Ovaries, Thyroid, Pituitary, Thymus	Infantilism, Amenorrhea, Asexualism, Sterility
	(c) Thyroid	Thyroglobulin (?)	Development of Gonads, Bones, etc.	Thyroid, Gonads, Pituitary, Thymus, Bones	Hypoplasia, Developmental Diseases
	(d) Pituitary (Ant. Lobe)	Tethelin	Development of Gonads, Bones, etc.	Adrenals (Cortex) Thyroid, Gonads, Bones	Diminutivism, Acromegaly, Acromicria, Hypogonadism

B. FUNCTIONAL ENDOCRINE STIMULANTS	(a) Liver	Antithrombin	Blood Coagulation	Liver, Parathyroids, Spleen (?)	Hemophilia, Purpura
	(b) Duodenum	Secretin	Pancreato-Biliary Stimulant	Duodenum, Pancreas, Liver	Indigestion, Pancreatic Insufficiency
	(c) Adrenals (Cortex)	Cortin	Muscular and Cellular Tone Stimulates Gonads	Adrenals, Muscles, Gonads	Sympathetic Irritability and Depletion, Virilism, (?) Addison's Disease
	(d) Placenta	Galactagogin	Galactagogue, Uterine Involutant	Placenta, Uterus, Mammæ	Agalactia, Subinvolution
	(e) Thyroid		Deaminization	Thyroid, Liver, Cellular Tissues	Malnutrition, Acidosis
	(f) Pituitary (Post. Lobe)	Hypophysin	Musculotonic, Fat and CH. Metabolism	Pituitary (Post L.) Pancreas, Thyroid	Obesity, Diabetes Insipidus
C. MORPHOGENIC ENDOCRINE ROLE (Still Questioned)	(a) Spleen	Colloidogenin (?)	Mineral Regulation	Spleen, Parathyroids, Liver	Tuberculosis
	(b) Thymus	Thymocrin (?)	Development	Thymus, Gonads, Bones	Defective Development
	(c) Mammæ	Mammin (?)	Anti-ovarian	Mammæ, Uterus, Ovaries	Hyperovarism, Menorrhagia
	(d) Pineal	Epiphysin (?)	(Not proved)	Pineal, Gonads, Brain	
	(e) Prostate	Prostin (?)	(Not proved)	Prostate, Testes, Thyroid, Pituitary, (Ant. Lobe)	Hypogonadism (?), Prostate Hypertrophy

* A Table Based Largely on that of Prof. E. Gley, of Paris.

IV

AN OUTLINE OF THE ENDOCRINE DISORDERS

(After that of Dr. James H. Hutton, of Chicago)

1. THE THYROID GLAND

Thyroid Hyperfunction—Hyperthyroidism

ENDOCRINE FINDINGS	Smooth, diffuse, symmetrical, vascular enlargement of the thyroid in Graves' disease. A nodular goiter in adenoma with hyperthyroidism. Hypersensitiveness to epinephrine and to thyroid extract. Persistent thymus or hypertrophy of lymphoid tissue generally.
GENERAL APPEARANCE	
Skin (Nails and Hair)	Thin, soft, moist skin. Circulation good; occasionally mottled erythema of neck and chest. Hair smooth, silky. Perspiration increased. Cutaneous excitability. Nails smooth and not brittle.
Structure (Bones, Muscles)	Delicate skeletal structure. Long, slender fingers. Increased mobility of joints. (Adenoma with hyperthyroidism occurs in persons of any skeletal build.)
CLINICAL FINDINGS	
Circulatory	Tachycardia; palpitation; vasomotor irregularities. Hypertension common in toxic adenoma; high pulse-pressure in Graves' disease.
Alimentary	Tongue variable. Attacks of diarrhea and vomiting with no apparent cause. "Nervous indigestion." Occasional constipation (spastic). Good appetite with loss of weight.
Respiratory	Shallow breathing; tachypnea; feelings of dyspnea.
Nervous	Nervous irritability extreme. Restlessness; apprehension; anxiety (phobias, obsessions). Insomnia. Psychomotor activity; fine tremor of hands and tongue. Sensations of heat and heat intolerance. Headache common ("pounding"). Reflexes increased.

Urogenital	Amenorrhea; occasionally diminished libido and potentia sexualis.
Special Sense	Exophthalmos; wide lid slits. Von Graefe's, Möbius', and Dalrymple's signs. (Swollen eyelids, pigmented lids.) Hearing sensitive.
LABORATORY FINDINGS	
Urinary	Polyuria; average solids and elimination.
Blood	Normal red count. Lymphocytosis, relative. (Said to occur in both hypo- and hyperthyroidism, but is more constant in hypothyroidism.) Eosinophilia occasional.
Metabolism	Basal metabolic rate increased. Undernutrition. Diminished carbohydrate tolerance. Temperature may be increased. Pulse-pressure increased by a lowering of the diastolic. This occurs most commonly in Graves' disease. The systolic pressure is frequently elevated in adenoma with hyperthyroidism, and is frequently mistaken for heart disease or hypertension.

Thyroid Hypofunction—Hypothyroidism

ENDOCRINE FINDINGS	Thyroid aplastic or atrophied, or colloid goiter. No increased sensitiveness to epinephrine. Thyroid extract well tolerated. Compensatory pituitary hypertrophy probable.
GENERAL APPEARANCE	
Skin (Nails and Hair)	Skin yellow like parchment or pale like alabaster. Malar flush. Myxedema. Nails thick, rough, wrinkled, dry, brittle, with white spots and longitudinal ridges. Extremities cold. Dermatosis common. Hair dry, scanty, brittle, lusterless. Outer third of eyebrows missing. Scant hairiness of the arms and legs. Perspiration reduced. When condition occurs early, teeth are irregular and of poor quality.
Structure (Bones, Muscles)	Retarded bony growth. Defective development of ossification centers. Short, thick, or deformed bones (fingers with blunt ends). "Rheumatism." Stiff joints, cracking noises in joints. Flatfoot very common.
CLINICAL FINDINGS	
Circulatory	Bradycardia; hypotension or hypertension. Constant chilliness; "dead" fingers. Sensitiveness to cold. Enjoy heat. Circulation poor.

Alimentary	Appetite poor or variable. Thick, coated tongue; dry mouth; hypocholia; constipation, gas, ptosis. Teeth soft, carious; pyorrhea common.
Respiratory	Respiratory oppression, slow respiratory rate. Asthma-like attacks. Occasionally symptoms of pressure on the recurrent laryngeal nerve.
Nervous	Apathy; poverty of thought and initiative; drowsiness; psychomotor retardation; melancholia. Marked sensations of cold. Asthenia. Headache dull and of "early morning" type. Reflexes reduced or absent.
Urogenital	Early puberty. Menses usually regular, profuse, painless. Amenorrhea occasionally; more often infiltration and menorrhagia. Diminished libido and potentia sexualis. Nocturnal enuresis and cystic irritability.
Special Sense	Deep-set eyes (enophthalmos); narrow lid slits; thickened lids. Tinnitus; otosclerosis. Giddiness. Nasal "catarrh." (Incipient cataract has improved under thyroid medication.)
LABORATORY FINDINGS	
Urinary	Variable output; low in solids and urea; high acidity; indican + +; many squamous epithelia.
Blood	Anemia usual. Leukopenia; lymphocytosis. Eosinophilia common.
Metabolism	Basal metabolic rate below normal. Obesity with general distribution; padding on dorsum of hands and feet, also in supraclavicular and dorsal cervical regions. Increased carbohydrate tolerance. Hypothermia. Blood calcium usually below normal but has no diagnostic import.

2. THE PITUITARY BODY

Hypo- and hyperfunctional states of the anterior lobe of the pituitary are usually divided, on a time basis, into pre- and post-adolescent. The anterior lobe is concerned with the growth and function of the osseous, voluntary muscle, and genital systems. A deficient function before puberty naturally results in a lack of development of these structures. The degree of departure from normal development is some measure of the functional deficiency of the anterior lobe, and indicates the time at which it occurred. A severe degree of deficiency results in short stature, small bones, and slight muscular development, while in cases of less anterior-pituitary involvement, the individual more nearly approaches normal in his bony

and muscular development. A mild degree of pituitary hypofunction results in but a slight lack of development. If the function remains normal until development is nearly complete and then becomes deficient, there is but little retardation of growth.

If the hypofunction begins after puberty when the osseous, genital, and voluntary muscle systems have attained nearly full growth, the deficiency makes itself manifest in a disturbance of these organs. The muscles are atonic, and the individual lacks strength and endurance. In the male there is loss of libido and potentia; in the female, a loss of libido and disturbances of the menstrual function—usually menorrhagia—occur.

Hyperpituitarism occurring before puberty results in overgrowth of the osseous, genital, and voluntary muscle systems; if this is sufficiently great, gigantism results. When the hyperfunction occurs after puberty, growth of the long bones is no longer possible, so the stimulating effect of the excessive anterior lobe secretion is exerted on the short, flat, and peaked bones, causing the typical picture of acromegaly.

The posterior lobe of the pituitary is concerned chiefly with the handling of carbohydrates and water. Its deficient function is marked by obesity. The fat is deposited in a characteristic way about the pelvic and shoulder girdles and upon the upper arms and thighs. There is little or no fat on the forearms or on the legs below the junction of the middle and lower thirds of the thighs, and there is none above the clavicles. This obesity occurs regardless of the age at which the deficient function begins.

Actual changes in the pituitary gland may bring about a series of localized symptoms distinct from the chemical changes. These are the pressure, or "neighborhood," symptoms and may be divided into two classes: Immediate (local) and intracranial (general) pressure effects. In the former, we look for the results of pressure on the structures in contact with the mass; while, in the latter, the results will be those found with any brain tumor, because of the increased intracranial pressure.

Among the former are well-marked eye symptoms, such as bitemporal hemianopsia (blindness of the outer temporal fields of vision) due to pressure on the optic chiasm. Usually, this affects only color at first, but later, form. When the tumor extends beyond the sellar edges, squint results from pressure on either the sixth cranial nerve (internal strabismus) or the third cranial nerve (external strabismus). As a result of still more extensive involvement, there may be pressure on the crura cerebri and disturbances of gait with a positive Babinski sign. Certain epileptoid attacks, the so-called "uncinate fits," are occasionally seen and probably are due to pressure on the uncinate gyrus.

Before the last of these pressure symptoms have developed, general intracranial symptoms will have supervened. These consist chiefly of a severe intractable headache, paroxysmal in character and often affecting both temples, with vertigo, vomiting (often of the projectile type), and failing vision. Later there are choked disc, progressive destruction of the visual fields, and ultimately true optic atrophy.

3. THE ADRENAL GLANDS (SUPRARENALS)

Addison's Disease—Hypoadrenia

ENDOCRINE FINDINGS	Various disturbances common to other glands. Status thymicolymphaticus. Hypogenitalism. Goiter. Dyspituitarism.
GENERAL APPEARANCE	
Skin	Skin and mucosa pigmented (from dirty yellow to dark brown), usually diffuse but accentuated in axillæ, about nipples, genitals, extensor surfaces of joints, and parts exposed to pressure. Dermographia (Sergent's white adrenal line).
Structure (Bones, Muscles)	Muscular asthenia extreme. Myotonia. Lumbar pains.
CLINICAL DIAGNOSIS	
Circulatory	Hyposphyxia (Martinet). Arterial hypotension; myocardial weakness. Syncope common. Vascular hypoplasia.
Alimentary	Meteorism; abdominal pain and tenderness; anorexia; nausea; vomiting; alternating constipation and diarrhea.
Respiratory	Subjective feelings of dyspnea. Tuberculous lesions or scars usual.
Nervous	Asthenia; stupor; drowsiness; insomnia frequent. Memory defects (excitation; irritability). Fainting spells.
Urogenital	Hypogenitalism.
Special Sense	Asthenopia.
LABORATORY FINDINGS	
Urinary	Defective output; reduced solids; high acidity; indican + + +.
Blood	Marked secondary anemia. Lymphocytosis.
Metabolism	Undernutrition. Hypoglycemia with increased CH tolerance (occasionally decreased). Reduced basal metabolic rate. The clinical syndrome of hypoadrenia presents symptoms similar to those of Addison's disease, but milder in form and degree. It is due to infection—general or focal, acute or chronic—prolonged mental or physical strain, or the overdosage of drugs such as arsenic or mercury as in the treatment of syphilis.

3A. ADRENAL CORTEX (INTERRENAL SYSTEM)

Hyperfunction

Due to tumors of the cortex. These are nearly always malignant.

ENDOCRINE FINDINGS	Adrenal cortex hyperplasia, aberrant interrenal bodies, and interrenal tumors (not detectable early). More common in the female, in whom they tend to produce male characteristics.	
GENERAL APPEARANCE	*Prepuberal*	*Adult*
Skin (Nails and Hair)	Premature development of hair. Acne; skin rough and coarse.	Hirsutism. Women show mustaches and beards and triangular arrangement of pubic hair with marked general hypertrichosis. General or patchy pigmentation. Acne.
Structure (Bones, Muscles)	Unusually rapid growth. Abnormal strength (Herculean infants).	Increased physical strength. Virilism ("masculine women").
CLINICAL DIAGNOSIS		
Circulatory		Skin warm and well vascularized.
Alimentary	Vomiting and diarrhea in late stages.	Nausea and vomiting in late stages.
Respiratory		Voice heavy and masculine.
Nervous	Abnormal psychomotor activity.	Egotistic, overbearing, irritable.
Urogenital	Pubertas præcox, including premature enlargement of genitalia; in young girls, mammary gland development and menstruation; in small boys, erections, pollutions, and change of voice years before such changes are due.	Irregularity of menstruation; amenorrhea. Unusually strong excitability. Hypertrophy of clitoris. Frigidity in late stage.
LABORATORY FINDINGS		
Metabolism	Obesity, especially of hips and abdomen. Rapid growth (emaciation and cachexia later)	Obesity common.

4. THE PARATHYROID GLANDS

Hyperfunction (?)

We are uncertain as to the existence of such a clinical state, but overdoses of the parathyroid hormone produce the changes indicated:

ENDOCRINE FINDINGS	Calcium deposits in muscles and tendons. Arterial calcification; hypertension. Renal glomerular changes. Hypercalcemia.

Hypofunction

ENDOCRINE FINDINGS	Parathyroids removed with thyroid. Hypoparathyroidism following thyroidectomy.
GENERAL APPEARANCE	
Skin (Nails and Hair)	Pallor of skin; dermographia; erythema. Angioneurotic edema. Nails brittle, ridged. Hair thin.
Structure (Bones, Muscles)	Defective growth of bones. Cramps of muscles; carpopedal spasm.
CLINICAL DIAGNOSIS	
Circulatory	Vasomotor disorders. Subnormal temperature; chilly sensation. Palpitation and shortness of breath.
Alimentary	Defective teeth. Gastric tetany. Dilation of stomach.
Respiratory	Tetany often induced by deep breathing. Laryngospasm.
Nervous	Mental disturbances; bizarre sensations; apprehension; fear of impending spasm or of being left alone. True tetany with tonic spasms—carpopedal, laryngeal, and occasionally general. Latent tetany with positive signs (Chvostek's, Trousseau's, Erb's). Paresthesias. Peripheral nerve hyperexcitability. Extremities frequently "go to sleep."
Special Sense	Tinnitus aurium. Tendency to cataract formation.
LABORATORY FINDINGS	
Urinary	Excessive loss of calcium phosphate (?)
Blood	Hypocalcemia. Anemia.
Metabolism	Deranged acid-base equilibrium; abnormal calcium metabolism. Reduced CH tolerance. Usually loss of appetite, constipation, and loss of weight.

5. THE SEX GLANDS (GONADS)

	Hypergonadism	*Hypogonadism Male—Eunuch*
ENDOCRINE FINDINGS	Ovarian or testicular tumors. Gonad hypertrophy.	Castration. Thyroid smaller.
GENERAL APPEARANCE		
Skin (Nails and Hair)	Early secondary sex hair growth. Premature dentition.	Pale, sallow, wrinkled skin. Feminine hair distribution. Hypotrichosis.
Structure (Bones, Muscles)	Rapid growth; partial early gigantism; early closure of epiphyses; premature ossification.	Increased height; tall, thin type usual; longer legs and arms. Small head; broad pelvis. Delayed epiphyseal union. Upper measure, *i.e.*, symphysis to vertex, exceeds lower, *i.e.*, symphysis to soles.
CLINICAL DIAGNOSIS		
Circulatory	Erethism.	Vasomotor atonia; cold extremities.
Alimentary		Variable.
Respiratory		Small larynx; child-like soprano voice.
Nervous	Mentality modified by premature sex development.	Loss of aggressiveness; neurasthenic state. Fears, phobias, depression.
Urogenital	Enlarged genitalia with premature function (pubertas præcox).	Castration early: Other sex organs hypoplastic; no sexual impulse. Castration late: Prostatic atrophy; gradual loss of libido and potentia.
LABORATORY FINDINGS		
Blood		Anemia usual.
Metabolism	Increased	Fat deposits on lower abdomen, buttocks, and breast; trochanteric obesity. Basal metabolic rate low.

Hypogonadism (Cont.)

	Male—Eunuchoid	*Female*
ENDOCRINE FINDINGS	Gonads aplastic or hypoplastic. Other endocrine glands, especially the pituitary, are involved.	Ovariectomy. Natural or premature menopause. This *may* be due to infections, acute or chronic, focal or general—or to operations that damage blood or nerve supply to ovaries.
GENERAL APPEARANCE		
Skin (Nails and Hair)	Pale, delicate, finely wrinkled. Hypotrichosis (feminine type).	Lack of secondary-sex hair growth.
Structure (Bones, Muscles)	Similar to eunuch.	Increased height before puberty. Long arms and legs. Long, thin hands.
CLINICAL DIAGNOSIS		
Circulatory	Similar.	Vasomotor disturb. (as in menopause).
Alimentary		Digestive imbalance. Nausea and vomiting resembling that of early pregnancy.
Nervous	Lack of normal emotions and willpower. Dull, relaxed, clumsy.	Nervousness; anxiety states; psychoses. Depression at menses.
Urogenital	Hypoplastic gonads; cryptorchidism; sterility; libido and potentia diminished or absent.	Before puberty: Infantile genitals and secondary sex characters. No mammary development. Complaints frequently date from a pelvic operation not involving ovaries, pelvic infections, or general infection as influenza, T. b., or lues. Amenorrhea, dysmenorrhea; colds at periods; paresthesias, etc.

LABORATORY FINDINGS		
Blood	Secondary anemia.	
Metabolism	Trochanteric obesity after age of 35.	Trochanteric obesity after 35. More often thinness. Low B.M.R.

6. THE PANCREAS

Diabetes Mellitus (Hypopancreatism)

ENDOCRINE FINDINGS	Pancreatic insufficiency (digestive as well as endocrine); hepatic detoxicative deficiency, adrenal irritability (sensitive to epinephrine).
GENERAL APPEARANCE	
Skin	Dry skin; pruritus. Susceptibility to furunculosis, carbuncles, etc.
Structure (Bones, Muscles)	Rheumatic muscular pains and cramps; protracted lumbar pain.
CLINICAL DIAGNOSIS	
Circulatory	Arteriosclerosis with intermittent claudication or diabetic gangrene.
Alimentary	Hypocholia; clay stools. Increased hunger and thirst. Rapid dental caries; pyorrhea with loss of teeth.
Respiratory	Air hunger (due to acidosis). Fruity odor of breath (acetonemia). Susceptibility to pulmonary tuberculosis.
Nervous	Myasthenia. Tendency to neuralgia. Neuritis with anesthesias, paresthesias, loss of reflexes, and trophic disturbances. Diabetic coma.
Urogenital	Polyuria, nocturia, glycosuria (ketonuria). Libido and potentia decreased later.
Special Sense	Early cataract.
LABORATORY FINDINGS	
Urinary	Glycosuria, increased density, acetonuria, hyperacidity.
Blood	Hyperglycemia. Anemia.
Metabolism	Reduced CH tolerance. Defective fat metabolism with lipemia, ketonuria, and acidosis. Basal metabolic rate may be increased. Emaciation often marked. Diabète maigre.

Except for the insufficiency of the islands of Langerhans that occurs in diabetes mellitus, pancreatic insufficiency is difficult of diagnosis. Many tests have been offered, but none are very satisfactory. Van den Bergh's test is used in some clinics; also Bassler's test.

7. THE THYMUS

Persistent Thymus—Hyperthymism

ENDOCRINE FINDINGS	Status thymicolymphaticus; enlarged thymus (X-ray). Hypoplasia of chromaffin system. In infants, an enlarged thymus demonstrable on physical examination may be shown also by the X-ray and *vice versa.*
GENERAL APPEARANCE	
Skin (Nails and Hair)	Parchment-like pallor of skin. Infiltration of subcutaneous fat. Heterosexual distribution of hair.
Structure (Bones, Muscles)	Anomalies of skull; heterosexual physical configuration (typus femininus in males and typus masculinus in females). Delayed epiphyseal closure. Muscular system relaxed and poorly developed. Osseous system fragile.
CLINICAL FINDINGS	
Circulatory	Congenital hypoplasia of cardiovascular system. Palpitation; dyspnea; cyanosis; sudden death. Very susceptible to infections, especially of the upper respiratory tract. A weakling in person and behavior.
Alimentary	Enlarged upper incisors; disproportion between median and lateral incisors.
Respiratory	Asthma. Asphyxial paroxysms. Thymic stridor.
Nervous	Asthenia; fatigability.
Urogenital	Hypoplastic genitalia; cryptorchidism.
LABORATORY FINDINGS	
Blood	Marked lymphocytosis; lymphatic hyperplasia.
Metabolism	Rapid changes in body weight. Temperature varies.

It is now quite generally believed that an early involution of the thymus is accompanied by premature puberty and that a persistent thymus, or failure to involute, is accompanied by delayed puberty. In other words, there is a reciprocal relation between the thymus and the gonads.

8. THE PINEAL BODY (EPIPHYSIS CEREBRI)

Hyperpinealism—Pineal Tumor

ENDOCRINE FINDINGS	Hypergenitalism; pressure effect upon pituitary (?).
GENERAL APPEARANCE	
Skin (Nails and Hair)	In children, precocious growth of hair.
Structure (Bones, Muscles)	Abnormal height and muscular development.
CLINICAL DIAGNOSIS	
Alimentary	Vomiting.
Nervous	*General* (brain). Increased intracranial pressure (internal hydrocephalus) with headache, vertigo, drowsiness, mental changes, choked disc. *Neighborhood* (tumor). Midbrain involvement causing various cranial nerve palsies, especially III, IV, VI, with diplopia. (Cerebral peduncle involvement with lesion in pyramidal tract.)
Urogenital	Premature puberty with hyperplasia of genitalia.
Special Sense	Secondarily affected by cranial nerve lesion.
LABORATORY FINDINGS	
Metabolism	Obesity. Less commonly cachexia and emaciation. Increased CH tolerance.

This is the syndrome accompanying teratoma of the pineal. Whether the syndrome is due to an excess of pineal secretion or to a withdrawal of its growth-inhibiting influence, is not definitely proved. Precocious puberty occurring in the presence of brain tumor enables us to diagnose pineal teratoma.

HARROWER PUBLICATIONS

MUCH of the success that has come to The Harrower Laboratory is attributable to its publications, one of which is before you now and should be satisfactory evidence of the worth-while character of its literature.

THE HORMONE is a monthly periodical reviewing the progress in this line, and, of course, emphasizing that phase of it which relates to the work and products of The Harrower Laboratory. The editorial aim is "to bring at least one practical, helpful idea to each reader each month at a time when it will serve best, and to make it easy of materialization," for an idea is useless unless it can be made to render some helpful service. Sent to physicians *on request.*

Harrower Products

THIS "Laboratory of Applied Endocrinology" was not started to compete with the packing houses or the large manufacturing pharmacists. The object was to have the facilities to develop new information, to perfect things that would come up, and to delve further into the very fascinating problem of finding endocrine remedies and of making them as good and as convenient as possible. This was originally a hobby developed in connection with the practice of endocrinology; now it is a vocation with clinical endocrinology as an interesting side-line!

While The Harrower Laboratory, Inc., has become an unexpectedly large institution and enjoys an important position in its special field, its aim remains the same as at its inception. Despite repeated requests and even urgings, we refuse to make endocrine products on a price basis, neither will we sell them save only in a fair, ethical fashion to and through the profession. The Harrower Laboratory manufactures no products that are put out by other firms as endocrine cure-alls, and in no case are its preparations offered to the laity. Further, no frozen, cold-storage raw endocrine material is used (except pancreas and stomach linings, which must be frozen to prevent autolysis or self-digestion). The fresh, government-inspected raw material is treated exactly as are meat products that are used for food. No imported glands are used.

In some instances, the Harrower line appears to physicians to be higher in price than other apparently similar products. This, indeed, is the case, for many imitative extracts and formulas have been put on the market merely to compete with the Harrower preparations. They lack not only originality but quality, and are competitive in price only.

Every doctor knows that the better his remedies, the better his results are likely to be; he also knows that the cheaper a product is, the poorer it is likely to be. Therefore, why jeopardize your reputation by trying to save your patients' money by prescribing something that is often described as "far cheaper than Harrower's but just as good"?

The famous Ruskin was right when he wrote: "All works of quality must bear a price in proportion to the skill, time, expense, and risk attending their invention and manufacture. Those things called dear are, when justly estimated, the cheapest." The writer confidently states that in many instances there is just enough difference between the Harrower products and some of the cheaper imitations *to make all the difference* between failure and success.

V

A SYNOPSIS OF ENDOCRINE SYMPTOMATOLOGY

(After that of Prof. Nicola Pende, of Genoa)

The Thyroid Gland

Athyroidia Totalis

Thyroid absent or sclero-atrophic.

Skin diffuse, myxedematous, infiltration of pale yellowish color, dry, furrowed, squamous, cold, senile. Sunken, atonic, drowsy-looking eyes. *Hair,* eyebrows, body hair sparse or slowly falling, opaque, dry. *Nails* atrophic, fragile. *Teeth* deciduous, carious.

Muscles flaccid, sclero-atrophic. Bones atrophied, sclerotic, fragile.

Genitalia atrophied only in advanced cases. In women, amenorrhea or menorrhagia; impregnation possible. In man, anaphrodisia, impotence.

Psychic, psychomotive, and psychosensorial reactions slow. Deep torpor, ideational, mnemonic, volitional, emotive deficiency. Tendency to hallucinations, depressive psychosis, and somnolence; speech slow, monotonous.

Cachectic condition masked by myxedematous infiltrations.

Serious slackening of basal metabolism and albumin combustion. High carbohydrate tolerance. Oliguria. Hypothermia, keen cryesthesia.

Slight anemia with low corpuscular value; mononucleosis, eosinophilia. Lowering of the autonomous tone, principally of the sympathetic.

Bradycardia, microsphygmia. Absence of sudor. Marked intestinal atony.

When occurring in periods of growth: Arrest of skeletal development, chiefly in the length of bones, hence trunk is thick-set; bones, tubular, short, stumpy. Arrest of dental, cranial, facial, genital, and intellectual development. Deficiencies in hearing and speech. Infantile balloon-like body.

Partial Hypothyroidism

Thyroid frequently very large—struma. Often palpebral edema, maximal in the morning.

Hair sparse, located high on the forehead and temples; usually dry and brittle. Absence or sparseness of hair on the outer third of the eyebrows; scorched appearance of eyebrows. Nails short or atrophic, either streaked or with whitish spots. Caries, or spontaneous, premature falling-out of the teeth. Scanty perspiration.

Tendency to myalgia, arthralgia, sclerosis of the articular and periarticular tissues.

Amenorrhea, leukorrhea, dysmenorrhea, menorrhagia; diminution of sexual appetite, but not constant. Frequent delay of puberal crisis, incomplete sexual development (uterus infantile; cryptorchidism). In some women, scanty lactic secretion. Apathy, a constant feeling of cerebral and muscular fatigue; phlegmatic temperament. Diurnal somnolence. Habitual headache.

Frequent obesity of moderate degree, often with accumulations of soft fat (pseudolipomas) in the supraclavicular fossæ, at the root of the tongue, around the breasts, and in the dorsal cervical region; padding on dorsum of hands, cuffing about wrists and ankles.

Tendency to slowing down of nutritional metabolism. Sugar and carbohydrate hunger.

Urine rather scanty, not very acid nor alkaline, frequently albuminuric and oxaluric. Extreme sensitiveness to cold, extremities often cold and cyanotic, tendency to chilblains and edema of the distal parts. Bradycardia, clinostatic bradycardia, arterial pressure variable—may be high or low. Tendency to premature atheroma. Excessive

development of the venous and lymphatic systems. Torpor of vascular reactions.

Anorexia. Habitual constipation. High degree of tolerance for iodine preparations.

Morbid Hyperthyroidism

Thyroid hyperplastic, richly vascularized or pulsating, sensitive.

Skin thin, glossy, warm, easily flushed and perspiring quickly, juvenile appearance, frequently with spots of brown pigment. Protruding eyes, with full rima palpebrarum, brilliant, with expressive looks. Not infrequently, circumscribed, acute, cutaneous edema. Rapid canities and calvities, generally circumscribed. Muscular atony and asthenia. Diffuse tumors. Bones thin, growth rapid in the direction of length. Tendency to periodic hydrarthrosis.

Genital atrophy. Mammary hypertrophy in males; atrophy in females. Diminution of sexual appetite. Impotence. Amenorrhea.

Excessive emotivity, hyperexcitability and psychic instability, cerebral restlessness. Continual need of motion. Insomnia.

Tendency to hallucinatory conditions, to conditions of mania and melancholia, and to hemicranial attacks.

Increase of oxidative processes, of albumin metabolism; loss of phosphorus and lime. Reduced carbohydrate tolerance. Marked and progressive emaciation, sometimes disappearance of fat from upper parts of body.

Extensive variations in metabolism. Nervous or alimentary glycosuria.

Tendency to hyperthermia; sometimes neurotic fever. Excessive sensation of heat. Acroerythrosis; extremities frequently hot, flushed, and perspiring.

Leukopenia with corresponding lymphocytosis.

Tachycardia with great instability of the pulse. Vascular erethism, with prevalence of vasodilatatory phenomena. Hyperidrosis.

Appetite good, often capricious. Variations of

gastro-intestinal secretory tonus; attacks of salivation, hyperchlorhydria, vomiting, diarrhea, mucomembranous enteritis.

Great instability of the tonus of the vegetative nervous system.

When occurring before puberty, skeletal development is accelerated in the direction of height, with premature uniting of the epiphyses; persistent juvenilism of form and habitus.

Constitutional Hyperthyroidism

Thyroid slightly increased in size, or even of normal volume.

In Infants: Scarcity of fat; hair plentiful, lustrous, with no tendency of the scalp to parasitism or eczema. Sexual physiognomic traits prematurely pronounced. Genitals prematurely developed. Eyes bright and intelligent.

Sleep scanty. Lymphatic glands undeveloped. (?)

Rapid ossification of the fontanelles. Premature or rapid development of the teeth, regularity in conformation, rarity of caries.

Premature development of speech, ambulation, and intelligence. Great vivacity and restlessness. Tendency to diarrhea.

In Adolescents: Very rapid increase in height and tendency to longilinear figure. Rather retarded development of the musculature. Rapidly occurring muscular fatigue. Tendency to the scoliosis of adolescence.

Premature development of the sexual instinct and sex characteristics; genital organs, however, usually not much developed. Frequent occurrence of psychic impotence and attacks of sexual frigidity.

Tendency to tachycardia and vasomotor neurosis. Susceptibility to bacillary infection (typhus, pulmonary tuberculosis).

In the Adult: Noticeable development of the pilary system, affecting mostly the hair of the head, eyebrows, and eyelashes. Margo supraciliaries rather prominent. Teeth excellently developed. Rapid growth of the nails.

Bodily sex characteristics strongly differentiated, but frequently with attacks of weakness and exhaustion. Bone development predominating in length, restricted in breadth.

Habitual leanness; fattening difficult. Muscular strength deficient, muscles slender. Rapid variations in the turgor of the tissues and in weight.

Persistent or prolonged juvenility of body and mind. Intelligence well-developed, quick, vivacious, with excessive development of the sense of criticism. Great emotivity and effectivity. Strong will-power, temperament later becoming changeable. Tendency to fits of depression and to pessimistic ideas. Classic neuro-asthenic characteristics.

Cardiac and vasomotor hyperexcitability, maximum in the vasomotors of the head and hands. Reduced sensibility to cold. Hands almost always warm and moist; hyperidrosis, especially of the extremities and armpits.

Tendency to atonic phenomena of the stomach. Defecation frequent and stool usually of soft consistency. Increased sensibility to iodine preparations.

In women, intermittent fecundity; lactic secretion plentiful; frequently down on the upper lip.

Number of red corpuscles and quantity of hemoglobin also above normal.

In Old Age: Disposition to senile tremor, Parkinson's syndrome, and attacks of cerebral congestion. In women, ready tendency to the appearance of symptoms of mild masculinism, and occasionally calvities of masculine type.

Hypertrichosis, hirsutism, hair coarse. In women, masculine arrangement of the hair. Teguments thick, not delicate like those of the constitutional hyperthyroid subject.

Genital function very active and premature.

Vascular hypertension. Disposition to vascular sclerosis, visceral sclerosis, and hyperplastic sclerosis of the nasopharyngeal, auditory, and laryngeal mucous membranes.

Total Hypopituitarism

Narcolepsy and lethargic condition.
Slackening of the pulse and respiration.
Great insensibility to pain.
Notable fall in temperature and blood-pressure.
Rapid progressive cachexia.

Partial Hypopituitarism

General adiposity (except above clavicles and below elbows and knees), frequently rapid and of considerable proportions, with predilection of the fat for the regions of the pubis, mammæ, thighs, supraclavicular fossæ, and antero-inferior abdominal wall. (In adolescents, the fat distribution is often like that in female adults.) Sometimes, especially in adults, there are circumscribed lipomatous masses (hands, feet).

Partial or complete inhibition of sexual functions, with hypogenesis or retrogression of the genitals.

In Infants: Deficient stature with excessive adiposity. Defective development, both of trunk and limbs, also in length and thickness of the bones. Irregular dentition, very small mandible, mouth narrow and circular in form.

Eyes either too close together or too far apart, orbits almost round, eyebrows sparse. Frequently the nose is rather small and nasal respiration difficult; adenoid growths in the nasopharynx. External genitals hypoplastic.

In Adolescents: Persistence of the puerile or feminine type of skeleton, recognizable by the delicate face, small hands with delicate tapering fingers, breadth of the pelvis, and pronounced lumbar lordosis.

Skin and cutaneous appendices of female type; skin, delicate and transparent, only slightly tinted; nails, delicate and pointed with only slightly developed lunulæ; hair, silky—that of armpits and pubis, fine and of feminine arrangement.

Teeth frequently irregular and superimposed in the

mandible by reason of the restricted alveolar margins; canines sometimes of the same shape as the incisors.

High carbohydrate tolerance. Sugar hunger. Hematic lymphocytosis.

Subnormal temperature. Slight hypotension. Slow pulse. Vagotonia. Muscular asthenia and very marked relaxation of the articular ligaments. Constipation.

Psychic apathy, somnolence, fits of distraction, hypoalgesia, loss of normal sense or great irritability and impulsiveness. Pituitary headache. In the milder forms, asthenic habitus and asthenia universalis.

Morbid Hyperpituitarism

Tendency to adiposity in advanced stages, or to cachexia.

Suppression of genital functions, sometimes premature, sometimes, at the commencement; sexual hyperexcitability and increased size of the external genitals.

Gigantism in youths, with excessive growth of bones (including the head) both in length and in breadth. In adults, osseous growth principally in breadth, most pronounced in face, hands, and feet (acromegaly). Tendency to circumscribed hyperostosis.

Hyperplasia of the connective tissues. Hypertrophy of the epidermis, cutaneous appendices, derm, and subcutis; hence skin thick and dense, not very mobile or transparent. Hair coarse; nails hypertrophic. Not infrequently universal hypertrichosis; in women, masculine hypertrichosis.

Polyuria and glycosuria frequent, but also frequently normal or subnormal carbohydrate tolerance.

Hematic lymphocytosis with eosinophilia.

Hypotension, more rarely hypertension.

Muscular asthenia. Apathy and somnolence, rarely restlessness. Painful acroparesthesia.

In tumor cases, sella turcica increased and deformed.

The Adrenals

Total Hypoadrenia

Intense diffuse melanoderma of the skin and of the mucous membrane.

Severe muscular adynamia. Cachexia.

Severe intellectual asthenia, incapacity for any mental work whatever; fits of psychic irritability or of melancholic depression.

Notable reduction of blood-pressure and severe cardiac atony. Hypothermia.

Coma-vigil. Tendency to sudden death.

Partial Hypoadrenia

Slight melanoderma of parts most exposed to the light and to lesions, or only scattered cutaneous spots.

Myasthenia. Disposition to Erb-Goldflam myasthenia.

Cardiovascular hypotension.

Status lymphaticus and hematic lymphocytosis.

In juveniles, habitus tending to long, slender, tubular bones; slight retardation and incompleteness of sexual development.

In pregnancy, disposition to intractable vomiting and eclampsia.

Morbid Hyperadrenia

In Fetal Life: Syndromes of external feminine pseudohermaphrodism.

In Childhood: Symptoms of pubertas præcox with macrosomia præcox; notable development of the muscles, but proportions infantile.

In Adolescents (and beyond arrest of genital functions): Hypertrichosis of masculine type, the female sex almost always being affected. Exaggeration of male characteristics at the expense of female, especially in hyperadrenia due to tumors of the cortex.

In the Adult: Some primitive hypertonic conditions of the arteries, with cardiac hypertrophy; certain early forms of arterial atheroma; transitory nervous glycosurias. Sexual development in women frequently accompanied by virilism; frequently by obesity.

Constitutional Hyperadrenia

Athletic and hypertensive constitution. In women, slight hypertrichosis of masculine type. In the period of growth, macrosomia with early sexual and intellectual development, adiposity, psychic hyperexcitability,

notable muscular strength, hypertrichosis (hyperfunction of the adrenal cortex).

The Parathyroids

Total Insufficiency

Acute incurable tetany (except by replacement therapy).

Tremors and epileptoid seizures. Sphincteral spasms.

Cachexia. Acidosis.

Hyperexcitability and vasomotor instability. Paresthesia.

Attacks of acute, circumscribed cutaneous edema and of gastric, intestinal, and sudoral hypersecretion.

Acute dystrophy of the hair, teeth, and nails.

Reduced carbohydrate tolerance.

Intelligence preserved. Hallucinatory delirium.

Partial Insufficiency

Chronic tetany, hyperexcitability of the motor nerves, mostly anodal. Mechanical hyperexcitability of the muscles.

Tendency to myotonic, choreiform, epileptiform phenomena; phenomena of psychic exaltation, hallucinations, delirium, acroparesthesia.

Hyperexcitability of the vegetative nervous system, with alternating crises of sympatheticotonia and vagotonia. Prevalence of phenomena of angiospasm and of hypertonia of the peripheral arteries. Face and extremities pallid and cold.

Laryngeal, gastric, and intestinal spasms.

Sudden appearance of gray hair and of acute alopecia—diffuse and circumscribed.

Dental disorders; fragility; defective development of the enamel.

Rapidly developing cataract. Underdevelopment and fragility of the skeleton, but without suspension of sexual development.

Angioneurotic cutaneous edema.

In women during pregnancy, childbirth, puerperium, and suckling, attacks of eclampsia and albuminuria.

Hematic mononucleosis.

Total Insufficiency

In prepuberty, excessive growth in length of the lower limbs; legs and arms appear too long for body. Hypoplasia of trunk, head, and face; height rather above the average.

Absence of evolution of the genitals, pubic hair, voice, secondary sex characteristics; hair and teeth well developed. Skin delicate and poor in pigment.

Apathy and psychic feminilism in men. Intelligence usually normal.

In adults, tendency to regression of the genitals and the secondary sex characteristics.

Many fine wrinkles in skin, especially about face; skin yellowish and parchment-like.

Tendency to adiposity, most marked on the pubis, around the mammæ, and on the thighs.

In women, frequently phenomena of nervous hyperexcitability, particularly vasomotor.

Partial Insufficiency

Scanty development of sex characteristics. In men, often female habitus; in women, indications of masculinism. Asexualism, frigidity.

In prepuberty, skeletal development somewhat excessive in direction of length, mostly excessive length of the lower limbs.

Adiposity (at times slight) most marked at the mons veneris, on the lower abdominal region, buttocks, breasts, upper eyelids. At other times, more diffuse and serious.

Hair plentiful. Skin pale and yellow, often prematurely wrinkled.

Muscles hypotrophic and hypotonic.

Apathy; intelligence preserved. Mental depression, patient often blue, nervous, and suspicious.

In women before periods, colds and sore throat; facial acne exaggerated; hands and feet "go to sleep" frequently. Occasionally a marked gain in weight occurs just prior to menses.

Morbid Hyperfunction

In Infants: Sexual and somatic development accelerated and premature. Premature consolidation of the epiphyses, causing ultimate stature below the average.

In Adolescents: Premature ossification of the epiphyseal cartilages. Excessive development of genitals and sex characteristics, frequently also of the muscles.

Chlorosis?

Osteomalacia?

Constitutional Hyperfunction

Sexual function very active, secondary sex characteristics very pronounced. In women, as also in men, the climacteric is rather delayed.

The Pancreas

Total Insufficiency

Severe glycosuria, frequently with polyuria. Acetonuria.

Absolute intolerance of carbohydrates; persisting, moreover, during fasting. Steatorrhea.

Increased disassimilation of albumin and fats. Cachexia.

A form of infantilism due to hypopancreatism (B. W. Bramwell).

Partial Insufficiency

Alimentary glycosuria, or slight chronic diabetes with adiposity. Excessive malassimilation of albumin, with no acetonuria. Normal intestinal absorption of albumin and fats.

The Thymus

Total Insufficiency

In Infants: Severe athrepsia. Skeletal nanism, with thick, short, deformed, fragile bones. Serious types of idiocy.

Partial Insufficiency

In Infants: Deficient development in the weight of the

organism with normal or premature morphologic evolution.

Bones slender, fragile, poor in calcium. Muscles hypotrophic and hyposthenic.

Tendency to nervous hyperexcitability, rachitic manifestations, and muscular dystrophy.

Morbid Hyperfunction

In Infants: Habitus plump, or even fat, with excessive nutrition. Facial complexion at times subcyanotic; at others, extremely pallid.

Attacks of asthma and laryngospasm.

Frequent hyperplasia of the lymphatic organs and of the spleen.

Remarkable dilatation of the left heart and arterial hypotonia.

Sudden death from occasional and very slight causes, as a fall, an anesthetic, etc.

In Adolescents and Adults: Habitus frequently longilinear with rather slender tubular bones; delayed ossification of the epiphyses; feminine configuration of the skeleton in males.

Suprapubic and axillary hypertrichosis; heterosexual location of hair and fat.

In women, frequently remarkable masculine development of the skeletal musculature.

Genital hypoplasia.

Skin pale and soft with a chlorotic tint.

Pronounced cardiovascular hypotonia, tachycardia, with dilatation of the left heart. Strong tendency to fainting fits upon slight psychic causes. Occasionally hypoplasia of heart and arteries.

Pronounced lymphocytosis, frequent reduction of hemoglobin.

Intolerance to thymus preparations. Excessive sensitivity to pilocarpin.

Enlargement of the thymus observable by the X-ray and by percussion (thymic zone displaced in an upward direction by breathing or by raising the head in a backward direction).

The Pineal Body

Total Insufficiency

In Infants: Macrogenitosomia præcox, frequently with obesity, or heterosexual manifestations.

In Adults: Obesity or cachexia.

Calcification of the gland visible by X-ray at the age of seven years.

Partial Insufficiency

Pubertas præcox.
Hypotrophy and muscular asthenia?
Obesity?

Harrower Service

FOR more than ten years, the slogan of The Harrower Laboratory has been "At *Your* Service." This means that any reasonable service that we may be able to offer *to the medical profession* will be attempted, regardless of inconvenience or cost.

This has made possible to many physicians a clinical cooperation that frequently has helped them out of some difficulty relating to a "problem patient." It has enabled others to develop ideas along these lines for which they had no facilities. To still others, it has meant cooperation in outlining a paper, preparing a bibliography, or getting certain specific information in this specialized field.

One of the outstanding features of this organization is its "individual" character. It is really a medical unit developed to produce information on the subject of endocrinology—to establish it, to materialize it, and to disseminate it.

A staff of three regular physicians, specializing in endocrinology, give their full time to those phases of the work of this organization that have to do with service to the profession. Correspondence on endocrine subjects and cases is welcomed, *and should be addressed to Glendale.*

The original statement made by the writer, which has been printed many scores of times and circulated by the million, is: "The aim of this organization is to develop information pertaining to the internal secretions in everyday practice and to facilitate the immediate and convenient application of this information by the medical profession."

VI

A CLINICOPATHOLOGIC CLASSIFICATION OF THE UNIGLANDULAR ENDOCRINE SYNDROMES

(After that of Prof. N. Pende, of Genoa)

I. THYROID

ATHYROIDISM	Complete myxedema in adults; Bourneville's myxedematous idiocy in growing subjects.
HYPOTHYROIDISM	Incomplete myxedema in adults, incomplete infantile myxidiocy, myxedematous infantilism, paroxysmal hypothyroidism, minimal hypothyroidism, monosymptomatic hypothyroidism.
HYPERTHYROIDISM	
Hormonic *(orthoplastic)*	Hyperthyroid temperament; attacks of puberal and menstrual physiologic hyperthyroidism; transitory emotive hyperthyroidism.
Dyshormonic *(metaplastic)*	Classic Basedow syndrome, Basedow-like syndromes, variable or paradoxic partial hyperthyroidism. (Léopold-Lévi's "thyroid instability".)

II. PITUITARY

APITUITARISM	Cachexia, hypophyseopriva. Pathologic lethargy.
HYPOPITUITARISM	Adiposogenital dystrophy—Frőhlich type. Pituitary nanism and pituitary infantilism. Pituitary feminilism.

HYPERPITUITARISM	
Hormonic *(orthoplastic)*	Hyperpituitary temperament. Slight eurythmic physiologic gigantism. Transitory physiologic hyperpituitarism of puberty and pregnancy.
Dyshormonic *(metaplastic)*	Acromegaly, pituitary gigantism, and acromegalo-gigantism.

III. ADRENALS

ANADRENIA	Acute anadrenia (asuprarenalism) of the following forms: Sudden death, choleric, apoplectic, pseudoperitonitic, myocardiac, encephalitic.
HYPOADRENIA	Addison's syndrome. Ferrannini's constitutional chronic angiohypotonia. Tuberculosis of the adrenals, periodic asthenia, hypoadrenia of pregnancy, etc.
HYPERADRENIA	
Hormonic *(orthoplastic cortic.)*	Athletic and hypertonic constitution.
Dyshormonic *(metaplastic medull.)*	Pseudohermaphroditism of adrenal origin. Transitory glycosuria of adrenal origin. Forms of adrenal arterionecrosis.

IV. PARATHYROIDS

APARATHYROIDISM	Severe spontaneous tetany, severe post-operative tetany.
HYPOPARATHYROIDISM	Slight or latent tetany, spasmophilia in infants and adults.

V. PANCREAS

APANCREATISM	Severe lean diabetes.
HYPOPANCREATISM	Slight fatty diabetes. Alimentary glycosuria. Pancreatic obesity.

VI. GONADS

AGONADISM	Syndrome of early castration. Syndrome of delayed castration.
HYPOGONADISM	Eunuchoidism of gerodermic form; feminilism of eunuchoid form; delayed hypogenitalism. Virilism of ovarian origin. Obesity of genital origin.
HYPERGONADISM	
Hormonic *(orthoplastic)*	Hypergenital temperament. Eurythmic pubertas præcox. Hypergenital nanism.
Dyshormonic *(metaplastic)*	Pubertas præcox of primary genital origin, with heterosexual symptoms. Chlorosis (?)

VII. THYMUS

ATHYMISM	Severe congenital idiocy (?)
HYPOTHYMISM	Pedatrophia with atrophy and softness of the bones and muscular atrophy (?)
HYPERTHYMISM	
Hormonic *(orthoplastic)*	Infantile macrosomia (?)
Dyshormonic *(metaplastic)*	Status thymicus in children and adults.

VIII. PINEAL

APINEALISM	Macrogenitosomia præcox of pineal origin. Pineal cachexia.
HYPOPINEALISM	Puberal precocity. Pineal obesity. Muscular asthenia and hypotrophy in young girls (?)

VII—A CLASSIFICATION OF PITUITARY DISORDERS

(After that of Dr. William Engelbach, of St. Louis)

I. ANTERIOR LOBE

A. Hypoactivity

1. Preadolescent
   a. *Aneoplastic*
   b. *Neoplastic*

   Diminutivism—Lorain-Levi type.

2. Postadolescent
   a. *Aneoplastic*
   b. *Neoplastic*

   Amenorrhea, dysmenorrhea (female). Loss of libido, impotence, etc. (male)—responds to anterior feeding. No posterior signs (*q. v.* below).

B. Hyperactivity

1. Preadolescent
   a. *Aneoplastic*
   b. *Neoplastic*

   Gigantism. No posterior signs.

2. Postadolescent
   a. *Aneoplastic*
   b. *Neoplastic*

   Acromegaly. No posterior signs.

II. POSTERIOR LOBE

A. Hypoactivity

1. Pars Intermedia (?)

   Polyuria. Reaction to liquor pituitarii. No signs of ant. l. or pars nervosa disorder.

2. Pars Nervosa

   Pituitary obesity (reduced B.M.R.), increased sugar tolerance. Polyuria and anterior signs absent.

B. Hyperactivity

Pituitary glycosuria. Increased metabolism, decreased sugar tolerance. Polyuria and anterior signs absent.

III. BILOBAR

A. Hypoactivity

Fröhlich's type with or without polyuria.

B. Hyperactivity

Gigantism or acromegaly with incr. B.M.R. and decr. sug. tolerance. No adiposity.

C. Heteroactivity

1. Ant. Lobe hyper- and Post. Lobe hypo-

   Gigantism or acromegaly with polyuria.

2. Ant. Lobe hypo- and Post. Lobe hyper-

   Genital aplasia, nanism, amenorrhea, etc., with pituitary glycosuria. Incr. metab.; decr. sugar tolerance.

VIII

DIFFERENTIATION OF PITUITARY DISORDERS

(After that of Dr. William Engelbach, of St. Louis)

PITUITARY—ANTERIOR LOBE

	Hypofunction		Hyperfunction	
	Preadolescent	*Postadolescent*	*Preadolescent*	*Postadolescent*
Type	Defective Growth. (Lorain-Levi dwarfism.)	Defective growth, except long bones.	Gigantism.	Acromegaly
Symptoms (Objective)	Short stature. Small extremities; acromicria (hand "en petit").	Normal or increased stature. Small extremities.	Normal or eunuchoid giant. Erect. Large and prominent extremities. Bones long and slender.	Short and stocky. Stooped. Torso longer than extremities. Extra large feet and hands, prognathism, club fingers; bones short, thick.
	Hypoplastic sex glands. Upper teeth often large.	Gonad dysfunction such as amenorrhea or metrorrhagia. Upper teeth large and occasionally separated.	Large, well-developed gonads. Upper incisor teeth large and separated. Hypertrichosis, especially on body.	Large, well-developed gonads. Separation of upper incisors constant; lower frequently also. Hypertrichosis especially on extremities.
Symptoms (Subjective)	Defective mentality. Sterility and impotence. Subnormal temperature, slow pulse, hypotension.	Average mentality. Sterility and impotence. Subnormal temperature, slow pulse, hypotension.	Indifferent and apathetic. Normal sex activity.	Temperamental, talkative. Bright mentality.
	Normal B.M.R. and sugar tolerance.	Normal B.M.R. and sugar tolerance.	Pulse, temperature, and blood-pressure normal.	Sex activity increased. Pulse, temperature, and blood-pressure normal.

PITUITARY—POSTERIOR LOBE

	Hypofunction	Hyperfunction
Symptoms (Objective)	Pituitary obesity.	Pituitary glycosuria.
	Obesity (girdle and mammary). Decreased B.M.R., increased CH tolerance, no hyperglycemia, polyuria, constipation.	Tendency to emaciation. Increased B.M.R.; decreased CH tolerance; glycosuria and hyperglycemia usual.
	Tendency to somnolence (hibernation). Dull mentality. Temperature subnormal, pulse slow.	No polyuria, intestinal spasticity. Nervousness and mental instability. Temperature normal, pulse rapid.

IX

THE RELATIONS OF THE ENDOCRINE ORGANS

	Cooperation	*Antagonism*
1. THYROID	Adrenals, Pituitary, Gonads, Liver	Thymus, Pancreas, Parathyroids
2. PITUITARY	Thyroid, Gonads, Mammæ, Adrenals	Pancreas, Duodenum,
3. ADRENALS Medulla Cortex	Thyroid, Gonads, Pituitary	Pancreas, Duodenum, Thymus
4. PARATHYROIDS	Pancreas, Liver, Gonads	Thyroid
5. GONADS Corpora Lutea	Thyroid, Adrenals, Pituitary, Mammæ, Placenta	Thymus, Mammæ, Pineal, Follicle
6. PANCREAS	Liver, Parathyroids, Duodenum	Adrenals, Pituitary, Thyroid
7. THYMUS	(?)	Gonads, Adrenals, Thyroid
8. PINEAL	(?)	Gonads
9. LIVER	Thyroid, Parathyroids, Pancreas, Duodenum	(?)
10. PLACENTA	Corpora Lutea, Mammæ	Follicle
11. DUODENUM	Pancreas, Liver	Adrenals, Pituitary
12. MAMMÆ	Pituitary, Placenta, Adrenals, Corpora Lutea	Gonads (F)

It is almost impossible to portray in an inflexible table or diagram a mind-picture of the hormonic actions and interactions. Not always does a hormone or the gland from which it originates act identically under different conditions. As we have already seen (Chapter II), many factors control the influences exerted by the endocrine glands upon one another and upon the body as a whole. One can, however, roughly show the generally accepted and principal actions of the various endocrine glands, and this has been done in the accompanying table and chart.

From the foregoing outline it will be clear that the majority of the endocrine glands divide themselves into two cooperative classes or systems that appear to balance one another. These are the sympatheticotonic or catabolic glands, including the adrenals, thyroid, pituitary, and gonads; and the vagotonic or anabolic glands, including the pancreas, parathyroids, and, perhaps, the liver.

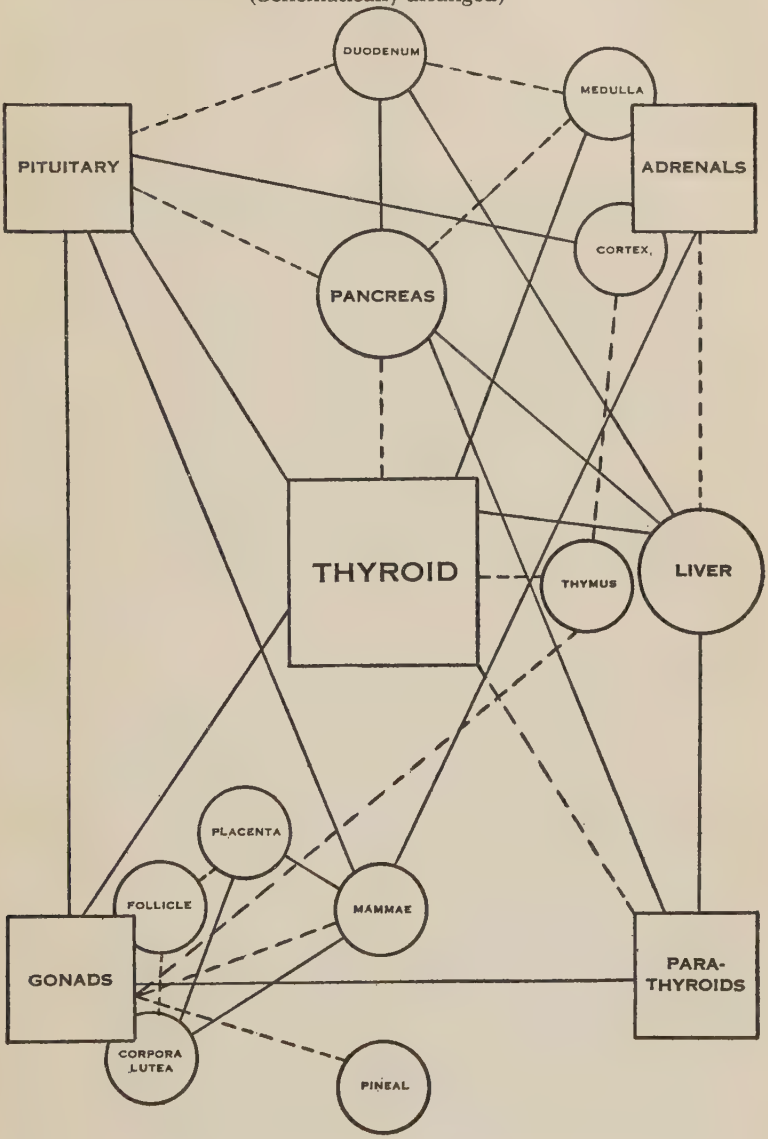
According to W. Langdon Brown ("Endocrines in General Medicine, 1927, p. 11), the adrenals, thyroid, and pituitary are predominantly catabolic and cooperate with the sympathetic division of the autonomic nervous system. They also cooperate with the gonads. On the other hand, the islet cells of the pancreas (Langerhansian) and the parathyroids are predominantly anabolic as is the parasympathetic division (vagus) of the autonomic nervous system.

The question has been asked: "Is the liver to be included with the vagotonic group because one of its important hormone functions is anabolic?" And it appears that, in view of the new knowledge that we now have regarding the detoxicative function of the liver, the answer will have to be in the affirmative.

These essential endocrine interrelationships were visualized in a schematic chart that appeared in my first book on endocrine matters, "Practical Hormone Therapy" (London, 1914, Bailliére, Tindall & Cox), and it may be of interest to reproduce this diagram here. It has been redrawn and brought up to date and should require no further explanation.

The Relations of the Endocrine Organs

(Schematically arranged)



X

CLINICAL AND LABORATORY PROCEDURES IN ENDOCRINE DIAGNOSIS

THE PRESENT-DAY STUDENT of clinical endocrinology is fortunate in being able to follow many careful workers who have illuminated the diagnostic pathway with their experiences.

Certain tests and signs are on record which, though by no means infallible indicators, serve to confirm the ideas that we may be building into a diagnosis.

It should be said here that practically no one of the tests or signs outlined below is of itself dependable evidence upon which to base a diagnosis.

Thyroid

The thyroid is one of the most important glands in the body, and consequently may be disturbed more frequently than any of the others. Since the thyroid is the chief chemical regulator, it manifests its irregularities in disturbances of metabolism. Accordingly, the estimation of the basal metabolic rate is invaluable as a differential diagnostic measure and a very accurate indicator of the thyroid function.

Basal Metabolism—There are a number of satisfactory machines on the market for making this necessary test. The method most frequently used is the gasometric. Since oxygen is absolutely essential to body chemistry, the measure of the oxygen intake over a definite period of time gives us an index of the chemical processes that are going on within the body. In order to get a correct estimation of the basal chemistry, or that amount of

oxidation which is required in order to meet the body's minimal needs without any extra call upon them, it is necessary that the patient be absolutely at rest, that there be no food in the stomach, and no mental excitement. Consequently, I prefer to make the test in the morning before breakfast while the patient is still in bed.

Full directions for using the different machines may be obtained from the manufacturers. Tables are supplied whereby the patient's height and weight may be converted into body surface and given the proper evaluation in the reading. After the mathematics of the test is carried out, the end-result is expressed in a *plus* or a *minus* figure. Zero has been used as an arbitrary starting point. Because there are some variations in all normal individuals, a leeway consisting of the difference between a *plus 10* and a *minus 10* is granted for these normals. The determination of the basal metabolic rate, or the B.M.R., is an invaluable laboratory aid in the diagnosis of variations in the thyroid function.

Thyroid Feeding—Patients demonstrate thyroid irritability or inactivity by their response to thyroid therapy. This principle may be utilized as a therapeutic test; in fact, my Thyroid Function Test is based upon it. Four doses of thyroid are given on each of three successive days. The doses are graduated so that ½, 1, and 2 gr. are given at suitable intervals on the first, second, and third days, respectively. Since an increase in the pulse-rate is a virtually invariable guide to thyroid irritability, a record of the pulse variations furnishes the information as to the patient's response. A convenient chart upon which to record the findings is illustrated on the next page. Complete and easily understood instructions are printed on the back of the chart.

The pulse should be taken a day before, and two days after the capsules containing the thyroid are administered. If there is little or no change in the pulse-rate, one may be assured that the patient is deficient in thyriod, *i.e.*, that the thyroid response is apathetic. If there is a slight increase on the second or third day, you have a normal individual whose thyroid may be

stimulated to some extent by thyroid feeding. If, however, there is a rapid and prolonged increase, the patient is positively hyperthyroid. It is evident that this test should not be given in chronic cases of hyperthyroidism.

No. *Date*

PULSE CHART

Name *Address*

	DAY BEFORE			FIRST DAY					SECOND DAY					THIRD DAY					DAY AFTER TEST					20 DAY AFTER				
	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6
160																											
150																											
140																											
130																											
120																											
110																											
100																											
90																											
80																											
70																											
60																											
50																											

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Any marked increase in the pulse is an indication to discontinue the capsules but to complete the pulse chart.*

Goetsch's Test—In 1918 Emil Goetsch used the fact that patients suffering from hyperthyroidism are usually sensitive to injections of epinephrine, as a means of measuring thyroid irritability. The response depends upon the fact that thyroid hyperactivity irritates the sympathetic nervous system. The patient should be absolutely at rest, and should be assured that the test will not inconvenience him. Blood-pressure, pulse, and respiration records are made, then ½ cc. of a 1:1000 solution of Endophrin (epinephrine hydrochloride—Harrower) is given subcutaneously. The observations are continued at five-minute intervals. The test is considered positive if the systolic blood-pressure rises from 10 to 50 mm. of mercury in the first five minutes. The pulse-rate is also increased at least twenty beats a minute. Usually the diastolic blood-pressure falls slightly. In half an hour there is another secondary rise, but to a smaller de-

*The materials and chart for a Thyroid Function Test will be sent gratis to any interested physician who makes request to Glendale.

gree. The test is of value as an associate measure only; and, of course, it is of no value in hypothyroid conditions.

Eye Signs in Hyperthyroidism, etc.—There are a number of signs on record that are sought for as of confirmatory value in exophthalmic goiter. They are the result of the oculo-muscular and sympathetico-tonic conditions present in this disease:

Exophthalmos, or proptosis, is the first and basal sign of exophthalmic goiter. The eye itself seems to be pushed forward from its socket, and when it is closed without special muscular effort the lids do not fully cover the eye (lagophthalmos).

Dalrymple's Sign—In Graves' disease the sclera may show above or below the cornea—more markedly and frequently below than above. It may be absent above but present below, or *vice versa.* It is distinctly a sign to be observed in the eye at rest in its primary position.

Von Graefe's Sign—Lagging of the upper lid in relation to the upper edge of the cornea in motion from above downward. In health, if the eye is directed upward and then follows an object, say the finger, brought down *slowly* to the horizontal meridian, the relation of the upper lid to the cornea is constantly preserved; but with the von Graefe phenomenon the upper lid lags and, if there is sclera showing between the upper lid and the cornea in the position of rest, it is seen to be wider as the eye descends from above downward.

Wilder's Sign—Another eye sign due probably to sympathetic irritability in hyperthyroidism is that of W. H. Wilder. It consists of a peculiar little jerk or twitching of the eyes at the instant of changing the movement of abduction to that of adduction. This sign can best be elicited by having the patient gaze intently at the end of the finger or at a pencil held about 18 inches in front of the eyes and moved with a slow, even pace from side to side so as to make the eye perform an excursion of abduction and adduction. When the eye reaches the limit of the excursion and changes from abduction to adduction, there will be seen a more or less

pronounced jerk or twitching before it regains its steady movement. Wilder says: "I have observed this as one of the earliest signs, even before those of von Graefe, Stellwag, or Dalrymple, and I have never failed to get it in any case of exophthalmic goiter that I have studied. However, it may be observed in some nervous diseases, such as multiple sclerosis and lateral sclerosis, in which one may also observe varieties of spastic tremors of which this seems to be an illustration."

Möbius' Sign—Still one more ocular sign of hyperthyroidism is an inability to keep the eyeballs converged. This is not always found, but is occasionally mentioned in the German literature.

Pituitary

Although the basal metabolic rate is decreased in hypopituitarism, that test alone cannot be used as an evidence of pituitary dysfunction. The clinical symptoms in pituitary disorders are most important. The distribution of fat, menstrual disorders, headache, and a tendency to lethargy must all be considered. Because one lobe of the pituitary controls the carbohydrate metabolism, a valuable test was devised on this basis.

Carbohydrate Tolerance Test—Weigh the patient. Multiply this weight (in pounds) by 0.8; the result is the number of Grams of dextrose to be fed the patient in the morning, without breakfast. It is usually given in the form of lemonade. Test the urine for sugar at hourly intervals four or five times. If no sugar appears, *i.e.*, if there is an increased carbohydrate tolerance, the case is likely to be one of pituitary sluggishness, and pituitary therapy is in order. (Following pituitary feeding, another test is likely to give a different response.)

Just as increased carbohydrate tolerance is suggestive of hypopituitarism, so a very low sugar tolerance is indicative of the opposite condition—hyperpituitarism—and not infrequently there may be glycosuria.

Cushing's Thermic Reaction—This test consists in the hypodermic administration of a solution of pituitary (anterior lobe). If the patient's pituitary activity is

insufficient, there will be a distinct rise of temperature and possibly sweating. This test is not used extensively.

Ocular Changes—Because of its location, at the base of the brain, a definite increase in the size of the pituitary gland may produce various eye symptoms. There may be bitemporal hemianopsia with the outer fields of vision impaired. This is discovered most accurately by perimetry. There may be also ocular palsies or alterations in the color vision. In well-advanced tumors epileptoid attacks, known as uncinate fits, may occur.

Sellar Radiography—An X-ray examination of the sella turcica, the bony cup at the base of the brain which holds the pituitary, is more frequently of value in a negative than a positive way. It is very possible to be misled in reading an X-ray picture if the position in which that picture is taken is not definitely known.* In other words, what is known as a lateral radiograph may vary considerably depending upon the operator. The presence of a small, irregular, or bridged sella may explain pituitary pressure. On the other hand, a large and open sella with well-divided clinoids, which would apparently allow sufficient freedom to the pituitary gland, may still enclose a pituitary sufficiently congested to cause pressure symptoms. I believe in making my own sellar reading, and the findings always are considered in conjunction with the patient's clinical symptoms.

Adrenals

A study of the arterial tension over a short period and under varying circumstances is an excellent guide to adrenal function, for the cardiovascular tone, including that of the heart muscle itself as well as that of the vessel walls, is largely dependent upon adrenal factors for its maintenance. Hypoadrenia ordinarily spells hypotension.

*My friend, Dr. D. M. Ghrist, of Glendale, Calif., has devised an apparatus by means of which a known, predetermined, and recorded position of the head is possible. It is of value in all head and sinus X-ray work.

Hyposphyxia—The circulatory syndrome to which Martinet, of Paris, gave this name is perhaps the most easily determinable of all the tests for hypoadrenia. This picture is the result of a modified form of circulatory asphyxia; hence the name. The stimuli that regulate the circulation, cardiac efficiency, and blood-pressure are deficient; consequently, a study of the manifestations of circulatory tone leads to information of value. Poor circulation, with bluish and cold extremities, myocardial asthenia, reduced blood-pressure (both the systolic and pulse-pressure), and other evidences of asthenia due to poor circulation, are commonly associated with adrenal insufficiency. Confirmation of this assumption follows the control of part or all of these hyposphyxic symptoms by adrenal therapy. It is quite common for patients with the functional adrenal insufficiency that so commonly follows influenza when the blood-pressure has been reduced from 30 to 50 points, to regain this loss following a course of Adreno-Spermin Co. (Harrower) for a few weeks. With the change in the circulatory manifestations comes a control of the general asthenic subjective manifestations. This is one of the most decisive and encouraging evidences of the value of this form of organotherapy.

Sergent's "White Adrenal Line"—A dermographical reaction was described by Emile Sergent, of Paris (*Endocrinology*, 1917, i, p. 18), and on it a convenient test has been based. The test consists in lightly stroking the skin over the abdomen with a blunt instrument, such as a fountain pen. A positive reaction consists in the appearance, within a few seconds or not more than half a minute, of a pale line or band following the course of the stroking. Gradually this becomes more and more distinct and extensive, so that eventually the line exceeds in size the actual area stroked. The white line attains its maximum clearness in about a minute and persists for two or three minutes before gradually disappearing. This, at least, is what is to be expected in well-defined cases of adrenal insufficiency—the only

instance in which the test has any real value. This sign does not occur in every case, and is therefore of only supplementary value.

Asthenocoria—Dr. C. F. Arroyo, of Tampa, Florida (*Med. Jour. and Rec.*, Jan. 2, 1924, cxix, p. 25), suggests a simple test which he claims to be of value in the determination of the presence of adrenal insufficiency:

"When exploring the pupillary reflex I found that in the iris of these cases, although reacting readily to light, the contraction was flabby, lazy, in a word, asthenic. By making the patient look at the light we see that immediately after the initial miosis the pupil starts to dilate slowly as if it does not want to, seems to try to contract again, but the dilatation gains the upper hand and, after a fight between miosis and mydriasis lasting for about forty seconds, the pupil remains dilated in spite of the persistence of the exciting agent. This sign is constant and present in all cases of hypoadrenia and in all its clinical forms. In the normal individual it does not appear, as I have investigated. All patients presenting this sign, which I should like to call *asthenocoria*, have been benefited by suprarenal medication."

Pancreas

The laboratory is of outstanding value in the diagnosis and study of diabetes mellitus. The examination of the urine for specific gravity, sugar, acetone, and diacetic acid is so well known as to need only the merest mention.

The estimation of the blood sugar is the most valuable index of pancreatic endocrine dysfunction. This test may be carried out in several ways, which are fully outlined in any laboratory manual. The variations in the blood sugar are an invariable guide to carbohydrate tolerance which, while not entirely under the control of the pancreatic internal secretion or the Langerhansian hormone, is regulated largely by it.

Acidosis, a condition commonly associated with advanced stages of diabetes but not infrequently found

under other circumstances, is studied by the estimation of urinary acid (acidimetry) and by certain technical procedures that will only be mentioned here:

1. Van Slyke's test of the alkali reserve.
2. Determination of the alveolar carbon dioxide tension.
3. A graduated plasma reaction (Sellard).

Parathyroids

Since the blood calcium reveals the principal evidence of hypoparathyroidism, its study (method of Kramer and Tisdall preferred) has become much more appreciated. Normal calcium figures are from 9 to 10 mg. per 100 cc. of blood. A decrease is an indication for parathyroid therapy, and, as is shown on page 102, Paracalcin promptly raises such an abnormal figure.

Liver

The hepatic detoxicative capacity is measured by certain liver function tests. As yet, no test is of value alone, but several together give dependable information. The tests used most are: Van den Bergh's test for the icterus index, both direct and indirect reaction; Widal's so-called "hemoclastic crisis"; Rosenthal's bromsulphalein dye elimination test, and the determination of the urobilinogen. None of these alone is sufficient.

A positive van den Bergh reaction for the presence of urobilin in the serum indicates excessive destruction of the blood in the spleen or elsewhere. The direct van den Bergh is a measure of the permeability of the liver cells as well as of the patency of the bile ducts.

Widal's reaction determines the ability of the liver to break down proteins into amino-acids with subsequent formation of urea. When this function is deranged, albumoses are formed after the ingestion of milk protein, and there is an allergic effect shown by decreased leukocytes and lowered blood-pressure.

Of the various tests of the capacity to eliminate dyes, Rosenthal's is the best. In minor liver disorders dye excretion is not reduced, but in the more severe conditions,

such as acute yellow atrophy and catarrhal jaundice, there is a marked retention.

To me, the difference between liver disease and liver dysfunction is important, and liver function testing to date appears to be chiefly a means of determining whether some serious disorder is present or not. Considering that the functional disorders are infinitely more common, it seems that some other tests should be more helpful. For instance, Glénard (1926) pointed out that the liver regulates the acid-base equilibrium; that the liver is a reservoir of alkaline ions intended to balance variations in the hydrogen-ion content of the blood. Elsewhere, reference has been made to sudden and marked drops in urinary acidity following injections of Anabolin, "as though an alkali had been given." It is suggested that this may be due to catalytic stimulation of the liver to release these alkaline ions. At least, the urinary acid index is frequently very high in hepatic toxemia.

Since a high urinary acidity and indicanuria commonly are concurrent, the examination of the urine for indican and indolacetic acid should follow acidimetry. To some, an Obermeyer test is too simple to be mentioned, yet indican and the protein waste products associated with it should be destroyed completely by the liver. W. M. Barton believes that spontaneous indicanuria is dependable evidence of the type of hepatic insufficiency that I term "hypohepatism." When the accompanying putrefaction is not marked, and consequently there may be only a trace of indican, Barton suggests "the provocative indican test." One mg. of indol is given in the morning on an empty stomach. Specimens of urine are collected every four hours and examined for indican. The liver should be able to destroy this amount so, if indican appears one may assume that hepatic detoxication is not normal.

Another useful urinary test is that for ammonia. The liver should transform into urea all the ammonia products brought to it. In hypohepatism, the ammonia may not be completely changed, and the amount excreted naturally increases. In 1911, I called attention to the fact that the total urinary ammonia (Malfatti's method) may be

increased three or four times the normal in cases with high urinary acidity and indicanuria. Another provocative test is suggested by Barton: Having determined the average twenty-four-hour ammonia excretion for several days, the patient is given 6 Gm. ammonium acetate by mouth. The twenty-four-hour specimen is studied for ammonia; considerable increase of the ammonia indicates an impairment of functional integrity.

Still another "test" is mentioned, but with trepidation since it consists in the use of Anabolin as a therapeutic diagnostic agent. Anabolin reduces certain functional hypertensions, particularly those in which toxemia results from defective hepatic detoxication. The supposition is that where Anabolin is of decisive value, the underlying cause of the toxemia and hypertension is in the liver. This may be supported by several of these urinary tests, or by the more generally accepted hepatic function tests.

Thymus

The X-ray examination of a persistent thymus is the best diagnostic confirmation. Fluoroscopy is best since the patient can be moved. Some years ago, I suggested that the thymic shadow could be identified more easily by comparing the shadows in the claviculo-sternal angles. X-ray therapy of a persistent thymus often gives striking therapeutic-diagnostic confirmation.

Harrower Ethics

IT is the policy of this organization to adhere to the principles of medical ethics as thoroughly as we know how: No secret formulas. No indications on labels. No package enclosures (except with ampules). No extravagant or untrue claims in our literature. No products to the laity except on proper prescriptions, and no correspondence with them. No endocrine materials in bulk or in tablets to manufacturers of patent-medicines.

The Harrower organization is actively engaged in endocrine research, making available to the profession new endocrine products only after *clinical* experimentation has undeniably proved their efficacy.

XI

ENDOCRINE PREPARATIONS, THEIR SOURCE, DOSAGE, AND INDICATIONS

THIS IS MERELY an outline. The references are to endocrine preparations only, such organotherapeutic products as the ferments (pancreatic and gastric), hemoglobin, bone-marrow, etc., being omitted. The data are arranged so that the essential facts may be found quickly and used for comparison. Naturally, preparations of The Harrower Laboratory are given prominence, for this information has been gathered to make clear the possibilities of endocrine therapy in routine practice. As the object of this institution is "to develop information pertaining to the internal secretions in every-day practice and to facilitate the immediate and convenient application of this information," these products—uniglandular and pluriglandular—have been perfected and produced with this aim in view.

It may be said with safety that products bearing the *Harrower* name are among the best available, many of them being original, and most of them being preferred by progressive physicians throughout the English-speaking world. They are made and sold on a quality basis, for, of all therapeutic products, those in this particular field cannot be made to meet price considerations.

1. THE ADRENAL GLANDS

A. The Adrenal Cortex

Source: The suprarenal capsules (adrenal glands) of food animals, chiefly cattle. Ratio, 1:6*. (Total adrenal substance is about 85 per cent. cortex.)

Active Principle: Cortin. This substance, announced in 1928, is the adrenal cortical hormone capable of "counteracting or destroying substances detrimental to the organism that may arise in one way or another, or of supplying one or more products that are essential to the functions of the body." (*Jour. Am. Med. Assn.*, Jan. 7, 1928, xc, p. 34.)

Standardization: Not yet standardized physiologically.

Relations: Cooperates with thyroid, gonads. Antagonizes pancreas.

Harrower Products: Uniglandular—Adrenal Substance (total), from 1 to 3 gr. t.i.d.

Pluriglandular—Adreno-Spermin Co. (tablets and solution).

> *Formula:* Adrenal total gr. ¼, Endothyrin gr. 1/12, Spermin Extract gr. 2, Calcium Glycerophosphate q.s. ℞ Adreno-Spermin Co. (Harrower)† No. C. (one hundred). Sig. *1, q.i.d. at meals and at bedtime.* (In acute cases, every three hours). The solution may be given simultaneously, 1 cc. daily or every other day, by intramuscular injection.

Explanation: These products are used in asthenic, hypotensive, run-down states where the adrenals have been overstimulated, as by chronic toxemia and acute infectious diseases (especially influenza), and where there are reduced oxidation, defective sympathetic tone, and a marked fatigue syndrome. Give early in acute conditions to avoid the "let-down," which is invariably an adrenal syndrome. Begin with 1 every three hours; later, 2, t.i.d. In chronic asthenia, the blood-pressure is an excellent guide to dosage and administration. With a blood-pressure (systolic) of 110, give 1, t.i.d.; of 100, 1, q.i.d.; and 90 or less, 1, five or six times a day. Forbid adrenal-stimulating foods and drugs, especially coffee and strychnine. *The adrenals already are overstimulated.*

Contraindications: Marked hypertension; hyperthyroidism.

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*This figure refers throughout to the ratio between the desiccated finished product and the raw gland.

†It is advisable to specify "Harrower," for there are now many cheap imitations. Endocrine remedies bought on a price basis alone, invariably are seconds.

B. The Adrenal Medulla

Source: The chromaffin tissue in the adrenals of cattle. Ratio, 1:13 (epinephrine to total adrenal, 1:860).

Active Principle: Epinephrine (hydrochloride). This substance, announced by Takamine and Aldrich in 1901, as adrenalin, is obtained as a crystalline powder, but is more commonly available in the form of a 1:1000 solution of the salt mentioned above. The adrenal medullary principle (known in physiology as adrenin) is intimately concerned with the control of the sympathetic nervous system and exercises an essentially vascular function—in contradistinction to the cortex, which has an antitoxic function.

Standardization: Epinephrine hydrochloride is a definite chemical. It is checked to standard potency by injecting 1-6500 gr. of the crystals into an anesthetized dog and comparing the kymograph tracing with that following the injection of a given amount of the 1:1000 solution.

Relations: Cooperates with post-pituitary. Antagonizes Langerhansian islets (insulin).

Harrower Products: Uniglandular—Endophrin Solution 1:1000 (ampules of 1 cc. each containing 1 mg. epinephrine hydrochloride; bottles of 1 oz.).

Pluriglandular—Sol. Adreno-Hypophysis Co., containing two parts of Endophrin (1:1000) to one part of Liquor Pituitarii (triple U.S.P. strength).

Explanation: Endophrin in 1:1000 solution is used locally in minor surgery for its vasoconstrictor effect; systemically in shock, collapse, and particularly in asthmatic attacks. The dose ranges from 5 to 15 min. by hypodermic injection. Sol. Adreno-Hypophysis Co. (Harrower) has the same indications and therapeutic possibilities as Endophrin. Its effect is not quite so strenuous, but the benefit lasts considerably longer.

The very long list of therapeutic indications includes: (1) *Local:* Conjunctivitis, coryza, epistaxis, hay-fever, hematemesis, hematuria, hemorrhoids, iritis, keratitis, laryngitis, rhinitis, urethritis, etc. (2) *General:* Hypoadrenia (Addison's disease), bronchitis, asthma, bronchial spasm, cholera, collapse, and shock during severe infections,

dysentery, Graves' disease, heart failure, and, perhaps, osteomalacia.

Contraindications: Hemoptysis, hypertension, diabetes, and pancreatic insufficiency.

2. CORPUS LUTEUM

Source: The corpora lutea of pregnancy from the ovaries of cattle and hogs (very difficult to separate corpus luteum from hog ovaries). Ratio, 1:5.

Active Principle: Lutein. This preparation, emphasized by Howard Kelly and Curtis Burnam in 1912, for a long time was believed to be the essential active principle of the ovary. This is not the case, however, for the ovarian stroma has an entirely different hormone, and the follicular principle (see page 106) is not produced by the corpora lutea but is found in the follicular fluid and elsewhere. The luteal principle is an ovarian antagonist, inhibiting estrus. It appears to balance the ovarian function and especially to overrule certain specific ovarian activities during pregnancy.

Standardization: Not standardized, but a colorimetric test of the essential lipochrome content is used.

Relations: Cooperates with thyroid, pituitary, placenta. Antagonizes ovaries (estrus), parathyroids.

Harrower Products: Uniglandular—Endoluteum (tablets, 2 and 5 gr., and in solution) from 2 to 5 gr. t.i.d.

Pluriglandular—Sol. Placento-Luteum Co. for use chiefly in hyperemesis gravidarum.

> *Formula:* A 4 per cent. nucleoprotein solution, each cc. of which contains the soluble, active principles of 15 gr. fresh placenta and 5 gr. fresh corpus luteum Dose: 1 cc. intramuscularly every twelve hours, or oftener.

Explanation: Corpus luteum is used in dysovarism with occasional benefit, which the writer believes is brought about "by the 'offense' caused to the ovarian hormone balance." In other words, the ovarian function is aroused in reaction to the corpus luteum. However, the luteal principle is of therapeutic value in menorrhagia; possibly also in the nausea and vomiting of pregnancy, and in

habitual abortion. In menorrhagia it may counteract the irritability of the ovaries responsible for the bleeding.

Since it is possible that, as has been suggested, menorrhagia often is a very early abortion occurring within the first four weeks of gestation, it is reasonable to employ Endoluteum in habitual abortion. (Use larger doses.)

In vomiting of pregnancy, many accoucheurs have reported interesting results from intramuscular injections of corpus luteum extract or of Sol. Placento-Luteum Co. (Harrower). These injections, continued for five or ten days, or longer, have frequently arrested the vomiting.

It will be recalled that Emil Novak (*Jour. Am. Med. Assn.*, Sept. 1, 1928, xci, p. 607) maintains that the menstrual cycle is brought about, not by the follicular hormone alone, but by that hormone in association with the corpus luteum, and that both are necessary. Consequently, in some forms of amenorrhea he gives double courses, one of about ten injections of the follicular hormone and the other of five or six injections of corpus luteum solution.

3. DUODENUM

Source: The upper eighteen inches of the small intestines of pigs (extracts from dogs are more active). It is extracted by means of hydrochloric acid from scrapings of the duodenal mucous membrane. Ratio, 1:12.

Active Principle: Secretin. This "original hormone" was first announced by Starling in 1902 as the "pancreatic hormone," since its principal activity is concerned with the completion of the digestive ferments in the acinous pancreatic cells.

Standardization: None.

Relations: Cooperates with pancreas, stomach, liver.

Harrower Products: Uniglandular—Duodenal Substance, gr. 5, t.i.d.

Pluriglandular—Pan-Secretin Co. (tablets—see under Pancreas, page 99).

Explanation: Secretin is a physiological pancreas stimulant. Although it is most active in experimental work when given by intravenous injection, it is not de-

stroyed by digestion. (Bear in mind that it is extracted by a strength of HCl far in excess of that normal in the stomach, and withstands boiling for a short time.) Its value in chronic pancreatic indigestion is very real. It is especially helpful in diabetes for its influence on digestion, and a number of articles show that it also has an effect on the pancreatic glycolytic influence.

Contraindications: Duodenal ulcer, hyperchlorhydria.

4. THE KIDNEY

Source: The kidneys of sheep and cattle. Ratio, 1:8.

Active Principle: Renin (?). There is still much doubt as to whether the kidneys produce an isolatable principle. However, there is evidence that they produce a substance with a special influence upon the glomerular physiology, which is said to be capable of increasing the permeability and secretory activity of the renal tubules.

Standardization: None.

Relations: No special relationships on record.

Harrower Products: Uniglandular—Kidney Substance (total), from 5 to 10 gr. t.i.d.

Pluriglandular—Renal Co. (tablets).

Formula: Desiccated Renal Glomerular Tissue and Pancreas (total) āā gr. 2½. ℞ Renal Co. (Harrower). No. C. Sig. *1 or 2, q.i.d., a.c.*

Explanation: Various forms of renal insufficiency, including ischuria, anuria, albuminuria, and some forms of Bright's disease, have improved following the use of these preparations. May be used as an adjunct in the treatment of disorders depending upon renal impermeability, such as ascites, dropsy, and uremia.

More recently (1928) it has been shown that the kidneys contain a principle that has a marked effect upon hemopoiesis and detoxication.

Contraindications: None.

5. THE LIVER

A. The Bile Salts

Source: The bile from cattle, or other animals. Ratio,

1:40. (Extr. Fel Bovis is a heavy syrup, one part representing eight parts of ox-gall.)

Active Principle: The two bile salts, sodium glycocholate and sodium taurocholate, although not endocrine principles, are used extensively in organotherapy inasmuch as they may be administered as "the most effective cholagogues known."

Standardization: Definite chemical salts.

Relations: Cooperates with liver and duodenum.

Harrower Products: Bile Salts Co. (tablets).

Formula: Six-grain sanitablets of repurified Bile Salts and Hepatic Substance (desiccated) in equal parts. ℞ Bile Salts Co. (Harrower). Sig. *1, q.i.d. between meals for three days, double dose for three days, treble dose for three days, continue until free bile appears with stool, then reduce to 3 a day for some weeks.* (Repeat this routine occasionally, especially in stubborn cases.)

Explanation: Used in hepato-biliary insufficiency and hypocholia. The increased flow of bile thus produced is mechanically beneficial in cholecystitis and gall-stones, and chemically helpful in constipation, alimentary toxemia, and mucous-enterocolitis. It is important to push the dose to effect; hence the step-ladder method outlined above.

Bile contains a certain substance known as mucinase, which is capable of preventing the coagulation of the intestinal mucus. In hypocholia this mucus is permitted to coagulate. This absorbs toxins and bacteria, thus making an irritated layer or poultice that favors mucous colitis.

Contraindications: Obstructive jaundice.

B. Hepatic Extract

Source: The parenchymatous tissue of the liver of all food animals. Ratio, 1:6 for ordinary desiccations; 1:30 for Hepatic Extract (Anabolin).

Active Principle: Anabolin. This substance, announced by us in 1925, is the liver detoxicating hormone capable of arousing and increasing the rate of the detoxicating functions in the liver cells. It has been shown to increase the capacity of the liver to destroy certain poisons, notably ammonium chloride, guanidine, and chloroform. It

is particularly active in stimulating hepatic circulation and function. Based on this, a means of standardization has become possible.

Standardization: By kymographic tracings. Each cc. of Anabolin Solution contains 12 units and is capable of reducing the blood-pressure of a 10-kg. dog by 12 points. (Anabolin Fortior is twice this strength and in similar circumstances 1 cc. will reduce the blood-pressure 25 mm. Hg.)

Relations: Cooperates with thyroid and parathyroids. Antagonizes adrenal medulla.

Harrower Products: Uniglandular—Liver Substance (total) from 5 to 10 gr. t.i.d. Hepatic Extract, Anabolin (solution in ampules—two strengths, Anabolin and Anabolin Fortior—and in tablets of 1 gr.).

Pluriglandular—Hepato-Splenic Co. (tablets).

> *Formula:* Hepatic Parenchyma gr. 2½, Splenocrin gr. 2, Anabolin gr. ¼, Boldine Hydrochloride gr. 1/60, Calcium Phosphorus Co. q.s. ℞ Hepato-Splenic Co. (Harrower). No. C. Sig. *1 after each meal and at bedtime.*

Explanation: Anabolin has been used chiefly in high blood-pressure of the functional variety, and for some years was believed to be essentially a "depressor hormone." Recent researches show that its influence upon blood-pressure is due to increased capacity of the liver to destroy poisons, including those that raise the tension. Anabolin, therefore, is not found to be active in normal cases and is of no value in the treatment of hypertension due to sclerosis and other mechanical causes.

The ideal procedure with Anabolin is as follows: Carefully study the patient, estimate the urinary elimination and renal efficiency, and (in cases with hypertension), having made a series of blood-pressure records, proceed with the usual preliminary hygienic and eliminative measures. Accomplish as much as possible by general methods. Then, after taking the blood-pressure, inject ½ cc. of Anabolin Solution intramuscularly. After the patient has rested half an hour, take a second blood-pressure reading. If it remains unchanged or has fallen only slightly, the second ½ cc. may be given. The next day the blood-pressure is studied again. If it has fallen from 10 to 30

points, an injection of 1 cc. may be given with another similar rest, and the blood-pressure taken again. If, however, the tension has fallen 50 or more points (and this is not infrequent), postpone the second injection another day.

If, after the second dose, the tension remains at its previous level or is reduced but slightly, the procedure is simple: Give 1 cc. daily for five or six doses, then the same amount every other day for two weeks longer.

Whether the patient has reacted markedly to the injection with a reduction of from 75 to 100 points (in cases where the blood-pressure originally was 250 mm. or more), or whether the blood-pressure change has been negligible, the dosage may be modified up or down as indicated. The preliminary care in the administration of the first few doses of Anabolin will avoid any discomfort from its inadvertent use where contraindicated.

It is neither necessary nor advisable to give more than 2 cc. of Anabolin Solution daily, nor is it an advantage to continue the injections for more than two or three weeks in any one series. In the majority of cases a preliminary series of injections will suffice, and the benefit may be prolonged and in many cases made permanent by continuing the remedy in tablet form—one tablet from one to three times a day.

In many cases Anabolin Tablets have been given alone, *i.e.*, with no previous injections, with almost as beneficial results as with the hypodermic method. The suggested dosage is one tablet the first day, two the second day, then three a day (usually at or near meals) for several weeks or months. Patients have been observed in whom, after decided benefit had been secured, the daily dose has been reduced to as little as one tablet twice a week, with the prolongation of the clinical betterment and control of the hypertension.

The pluriglandular formula, Hepato-Splenic Co. (Harrower), now contains Anabolin and is used to continue treatment that has been started with Anabolin and to maintain, over a long period, a better control of the hepatic detoxicative function.

Contraindications: Nephrosclerosis, renal efficiency

(R.E. test with phenolsulphonephthalein) 35 per cent. or less, compensatory (mechanical) arterial hypertension.

C. Liver Extract (Hemopoietic).

Source: As above. Ratio, 1:45 for the hemopoietic fraction.

Active Principle: Hemopoietin. A similar substance, announced by E. J. Cohn and his associates in 1927, is the hemopoietic liver principle capable of stimulating the production of reticulocytes by the hemopoietic mechanism and with a record of hemopoietic wonders that is without parallel in organotherapeutic practice.

Standardization: Not physiologically standardized, but a clinical test involving the red-cell count and the reticulocyte index is used to determine its hemopoietic activity.

Relations: None of special note.

Harrower Products: Uniglandular—Heparhemin (Liver Extract, hemopoietic) from 30 to 60 gr. b.i.d.

Pluriglandular—Heparnucleate (powder in tubes).

> *Formula:* Heparhemin (a water-soluble, hemopoietic liver principle) 3.5 Gm., sodium nucleate 0.8 Gm. with lactose q.s. ℞ Heparnucleate, twelve 4.5-Gm. tubes. Sig. The contents of one or two tubes, with milk, soup (not hot), or orange juice.

Explanation: The use of liver extract in pernicious and other forms of serious anemia has revolutionized our conception of this disease and has awakened the interest of many physicians in the possibilities of organotherapy. Heparnucleate, a combination of the hemopoietic liver extract and sodium nucleate (based on the work done in the University of Oregon in 1927) is given in all forms of serious anemia as well as in pernicious anemia. The average dose is one 4.5-Gm. tube daily. It is an advantage, however, to give the contents of two tubes daily for the first six days, for it is believed that in this way materials can be accumulated that the body can utilize in proportion to its capacity or need. (For further information see page 131.)

Contraindications: None. (Heparnucleate is not a remedy for the simple anemias in which the red-cell count is 3,500,000 or more.)

6. THE LYMPHATIC GLANDS

Source: The lymphoid tissue of calves and young animals. Ratio, 1:5.

Active Principle: Not known. However, some writers believe that there is a principle in lymphatic tissue which, when administered in certain cases, encourages or supplements a seemingly necessary activity of these tissues in the body which, especially in children under certain circumstances, have been increased in size.

Standardization: None.

Relations: Cooperates with spleen, parathyroids, and possibly thyroid.

Harrower Products: Uniglandular—Lymphatic Substance (total), from 5 to 10 gr. t.i.d.

Pluriglandular—Lymphatic Co. (tablets—not generally stocked).

Formula: Desiccated Lymphatic Substance gr. 2, Spleen gr. 1½, Thyroid gr. 1/16, with Calcium Lactate q.s. ℞ Lymphatic Co. (Harrower) No. C. Sig. *2, t.i.d. with meals.*

Explanation: This product continues to be used by a very few physicians with what they claim to be remarkable alterative and reconstructive effects in children of the lymphatic type, especially those with large and recurrent adenoids and hypertrophied tonsils, and in bleeders.

Contraindications: None.

7. THE MAMMÆ

Source: The parenchymatous tissue of the udders of cows. Ratio, 1:4.5.

Active Principles: Mammin (not yet definitely isolated). Mammary extract is known to exert two quite decided physiological effects—it is a galactagogue (and uterine involutant), and it is an ovarian antagonist.

Standardization: None.

Relations: Cooperates with placenta. Antagonizes ovaries.

Harrower Products: Uniglandular—Mammary Substance (total) from 2 to 10 gr. t.i.d.

Pluriglandular—(a) Placento-Mammary Co. (as a galactagogue and uterine involutant).

Formula: Desiccated Placenta gr. 2, Mammary Substance gr. 1½, Pituitary gr. 1/3 with Calcium Phosphorus Co. q.s. ad. gr. v. ℞ Placento-Mammary Co. (Harrower). No. C. Sig. *2 sanitablets t.i.d. at meals for the first two weeks; thereafter, 1, t.i.d.*

(b) Mamma-Pituitary Co. (as a uterine decongestant, especially at the menopause).

Formula: Mammary Substance, gr. 2½, Ergotin (Bonjean) gr. ½, Pituitary gr. ¼ with Calcium Phosphorus Co. q.s. ad. v. ℞ Mamma-Pituitary Co. (Harrower). No. C. Sig. *1, t.i.d., a.c.; double three days before and during flow; omit for one week; repeat.* (Occasionally give 2, every three hours during heaviest flow.)

Explanation: Mammary organotherapy has been the subject of much critical difference of opinion, possibly because the mammary principle has not yet been isolated as have many other endocrine products. Empirical experience over many years in literally tens of thousands of cases establishes quite definitely the two outstanding therapeutic possibilities referred to above.

On page 98 reference is made to an unusually effective cyclic method of administering ovarian stimulating organotherapy. The same method of dosage applies in the treatment of menorrhagia. This explains the special dosage suggestions made above, which are visualized in the subjoined chart.

It may be well to compare this with the chart on page 98 and note the difference.

The advantage of combining certain substances that are known to exert a synergistic effect with mammary extract (placenta, when used as a galactagogue; and pituitary and ergotin, when used as a uterine antihemorrhagic) is nowhere more decided than in the foregoing preparations. (The ergotin in this formula is in dosage ordinarily inactive alone but it "directs the influence of the associated remedies to the uterus.")

Contraindications: Hypo-ovarism, infantilism, amenorrhea. *Note:* It is not advisable to give the galactagogue formula until after delivery.

8. THE OVARIES

Source: The ovarian stroma from the ovaries of cattle and, occasionally, of hogs. Ratio, 1:7.5.

Active Principle: Folliculin, Oophorin. The former substance, announced by Doisy and Allen in 1925, is "the essential female sex hormone" capable of bringing about rut or estrus in ovariectomized animals (see "Plestrin" under Placenta on page 106). The ovarian stromal principle differs materially from the luteal principle (see page 88) and also from Folliculin. In other words, neither the luteal nor the follicular principle is responsible for the therapeutic worth of ovarian extract.

Standardization: None.*

Relations: Cooperates with thyroid, pituitary, adrenals (especially cortex.) Antagonizes mammæ and thymus.

Harrower Products: Uniglandular—Ovary (whole), from 3 to 5 gr. t.i.d. Ovarian Residue, same dosage. Endovarin (tablets of 2 and 5 gr., and in solution).

Pluriglandular—(a) Thyro-Ovarian Co. (tablets and solution) for dysovarism, amenorrhea, dysmenorrhea, menopause, etc.

Formula: Endovarin gr. 2½, Endothyrin gr. 1/12, Pituitary (total) gr. ⅛ with Calcium Phosphorus Co. q.s. ad. gr. v. ℞ Thyro-Ovarian Co. (Harrower). No. C. Sig. *2, t.i.d., a.c., for ten days before menses; omit for ten days at onset of menses; 1, t.i.d. until ten days before menses.* (In total amenorrhea: 1, t.i.d. for one week; 2, t.i.d. for two weeks; omit a week; repeat.)

(b) Adreno-Ovarian Co. for dysovarism with asthenia and hypotension.

Formula: Thyro-Ovarian Co. gr. 5 with Adrenal Gland gr. ½. ℞ Adreno-Ovarian Co. (Harrower). No. C. Sig. same as above.

*There are ways of standardizing ovarian and other endocrine substances, which are essentially gravimetric and not physiological.

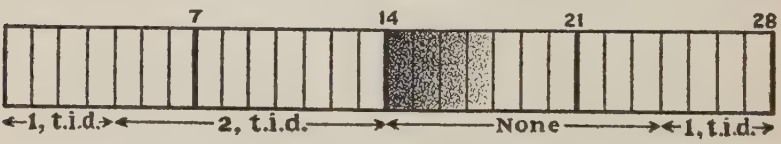
(c) Gonad-Ovarian Co. for infantilism, asexualism, marked amenorrhea.

Formula: Thyro-Ovarian Co. gr. 3, Spermin Extract and Pituitary (ant.) āā gr. 1½. ℞ Gonad-Ovarian Co. (Harrower). No. C. Sig. same as on previous page.

(d) Thyro-Pancreas Co. with Ovary for hypertension at the menopause. See under Pancreas, page 100.

Explanation: On page 16 there appears an explanation of the importance of "the ovarian trinity" and the necessity for pluriglandular therapy in ovarian dysfunction. A great many difficulties are based on dysovarism and, in addition to the ordinarily accepted disturbances of menstruation and the menopause, numerous neuroses and even psychoses connected with irregular menstruation are benefited by this treatment. It is of advantage also in cases of digestive disturbances, circulatory imbalance, rheumatism, and obesity that are shown to be related to dysovarism. In such circumstances the attempt is to modify a factor that is interfering with functions related to the disease present. In most cases of this type, the extent of the difficulty comes about through the intimacy of the thyroid with the ovaries. For this reason such treatment is also an advantage in many cases of goiter and epilepsy. In that phase of the latter condition sometimes called ovarian epilepsy, Gonad-Ovarian Co. (Harrower) is the preferred formula because of its large pituitary content.

Emphasis should be laid upon the cyclic method of dosage of (a), (b), and (c), mentioned previously. This idea, visualized for emphasis in the subjoined illustration,



enables one to concentrate the beneficial influence of the remedy at the times when it is most likely to be needed and effective.

Contraindications: Pregnancy, hyperovarism, erotism, nymphomania.

9. THE PANCREAS

A. Pancreas Tail

Source: Sweetbreads from hogs and cattle. Ratio, 1:5.

Active Principle: Insulin. This substance, announced by Banting in 1922, is the pancreatic internal secretion, originating in the islands of Langerhans in the tail of the pancreas. Experiments show that there is another substance in the pancreas that exerts an undoubted effect.

Standardization: By the effect upon the blood-sugar curve. Each unit enables a patient with severe diabetes to metabolize from 1 to 2.5 Gm. of additional glucose.

Relations: Cooperates with duodenum and parathyroids. Antagonizes adrenals.

Harrower Products: Uniglandular—Pancreas Gland (total) from 5 to 10 gr. t.i.d.

Pluriglandular—Pan-Secretin Co. (tablets).

Formula: Pancreas Islets (tail) gr. 3½, Secretin Extract (duodenal) gr. 1½. ℞ Pan-Secretin Co. (Harrower). No. C. Sig. *from 1 to 4 sanitablets with food three or four times a day.* The dosage of this formula is best varied in relation to the blood or urinary sugar.

Explanation: These products are used chiefly in diabetes, which is a true type of pancreatic endocrine insufficiency. Insulin exerts a pharmacologic effect that assists in the burning of sugar. The unitage given should correspond with the CH tolerance and the amount of CH administered. Many experiences show that this effect is artificial and independent of the pancreatic function. On the other hand, Pan-Secretin Co. (Harrower) is given by mouth for its homostimulative or restorative effect—the pancreas tail for its influence upon the corresponding structure in the pancreas, and the secretin for its influence upon the acinous or digestive functions of the pancreas. Pan-Secretin Co. has no such influence as insulin (see page 18). It is dependent upon the responsiveness of the patient's pancreas; hence its value depends upon this. It is less effective in diabetes in children, and more effective in middle-aged or elderly patients. In view of these facts, the dosage naturally varies, and it is an advantage to give Pan-Secretin Co.

in an irregular step-ladder fashion in order to determine the response. It does not take the place of insulin, but may be used to supplement it. Dietetic, detoxicative, alkalinizing, and other measures also are indicated.

Contraindications: In the rarer type of hepatic diabetes it seems to be a detriment.

B. Pancreas Total

Source: Same as above.

Active Principle: ?

Standardization: None.

Relations: Same as above.

Harrower Products: Uniglandular—Pancreas Total, from 5 to 10 gr. t.i.d.

Pluriglandular—(a) Pancreas Co. in sympathetic irritability, hypertonus, hyperthyroidism, etc.

Formula: Adrenal and Pituitary (total) āā gr. ½, Endovarin gr. 1, Pancreas (total) gr. 3. ℞ Pancreas Co. (Harrower). No. C. Sig. *1, q.i.d., a.c.* (In acute cases, in severe hyperthyroidism, increase dose to 6 or 8 a day for a time.)

(b) Thyro-Pancreas Co. with Ovary (or Spermin) in functional endocrine hypertension.

Formula: Pancreas (total) gr. 2, Endothyrin gr. 1/12, Spermin Extract gr. 2 (or Endovarin), with Calcium Phosphorus Co. q.s. ℞ Thyro-Pancreas Co. w. Spermin—or Ovary, as desired—(Harrower). No. C. Sig. *1, q.i.d. at meals and at bedtime.*

(c) Renal Co. in renal impermeability, albuminuria, etc. (see under Kidney, page 90).

Explanation: The pancreas undoubtedly has a second internal secretion, which influences the sympathetic system and the nutrition rather than the carbohydrate metabolism (as is the case with insulin). For example, pancreatectomized dogs whose carbohydrate metabolism was nicely controlled with insulin were thin and abnormal, but on supplementing the treatment by feeding pancreas they promptly gained their weight and strength. (See footnote on page 19.) The marked antagonism between the pancreas and the adrenals makes pancreas therapy valuable in conditions

of adrenal irritation, such as sympatheticotonia and hyperthyroidism. This applies equally in certain forms of endocrine hypertension, especially in women at the menopause, where a part of the difficulty is believed to be due to adrenal irritability. The formula, Thyro-Pancreas Co. with Ovary (or, for men, with Spermin), frequently will control a hypertension of this character as effectively as any means available. The addition of total pancreas to renal glomerular tissue (see page 90) is made for the purpose of encouraging simultaneously the pancreatic, detoxicative, and sympathetico-sedative influences.

Contraindications: Addison's disease.

10. THE PARATHYROIDS

Source: The parathyroid glands of cattle. Ratio, 1:6.

Active Principle: Paracalcin, Paroidin, Parathormone. The active substance, first separated by Adolph Hanson, of Minnesota, in 1924, is the essential parathyroid hormone. It regulates the amount and character of the calcium in the blood and, indirectly, is responsible for a certain phase of cellular detoxication, presumably through this calcium-regulating influence.

Standardization: By estimating the average influence of given amounts upon the blood-calcium index in dogs of known weight. (No less than sixty-three blood-calcium estimations are required in the standardization of each batch of Paracalcin!)

Relations: Cooperate with liver, spleen, and, perhaps, thyroid. Antagonize pancreas.

Harrower Products: Uniglandular—Parathyroid Substance (total) from 1/10 to 1/20 gr. t.i.d.* Paracalcin (tablets): One tablet equals one unit. Paracalcin Solution: Each ½ cc. equals 10 units.

Pluriglandular—Para-Spleen Co. (tablets and solution.)*

*Recently it has been suggested that very large doses of parathyroid are of benefit, especially in arthritis. The special formula known as Para-Spleen Fortior contains 1 gr. of true parathyroid (desic.) with 4 gr. of Splenocrin powder. The suggested dose is one tablet t.i.d. (See page 138.)

Formula: Desiccated Parathyroid *(true)* gr. 1/20, Splenocrin gr. 2; Spermin Extract (from Leydig cells) gr. 1, and Bile Salts gr. ½, with Calcium Phosphorus Co. q.s. ℞ Para-Spleen Co. (Harrower). No. C. Sig. *1 sanitablet q.i.d. at meals and at bedtime.*

Explanation: These products are valuable in two distinct types of disorders: Toxic conditions like Parkinson's disease, tetany, etc.; and the less marked but, perhaps, more protracted toxic dyscrasias, such as hemophilia, chronic ulcers, etc. It is also of value in bleeding from the uterus, or after tonsillectomy, etc.

In all types of tetany and Parkinson's disease, give ½ cc. of Paracalcin Solution intramuscularly daily with Paracalcin or, preferably, Para-Spleen Co. (Harrower), 1 tablet q.i.d. at meals and at bedtime. Treatment must be continued for a long time.

In chronic ulcers, as, for example, ulcers of the leg, ulcerative colitis, chronic sinusitis (only in cases with proper drainage), etc., give Para-Spleen Co. (Harrower) 1, q.i.d. with or without injections of the same solution. The synergistic action of spleen upon the calcium-regulating influence of parathyroid is well established and the combination is a decided advantage over parathyroid alone.

Contraindications: None.

11. THE PINEAL BODY

Source: The pineal glands (epiphysis cerebri) of cattle. Ratio, 1:7.

Active Principle: Not found. Some years ago pineal gland was suggested in the treatment of certain cases of pineal tumor and in hastening delayed maturity. It has been recommended in the treatment of mentally deficient children without physical stigmata.

Standardization: None.

Relations: Adrenal Cortex (?), Gonads.

Harrower Products: None.

Explanation: Pineal therapy is not generally an effective measure. In defective children, other endocrine products are equally or even more beneficial; for example,

Antero-Pituitary Co. (Harrower). (See below.) Pineal Substance is a most expensive product for "it takes approximately 5000 pineal glands of cattle to make one pound of the available extract."

12. THE PITUITARY GLAND

A. The Anterior Lobe

Source: The pituitary glands (hypophysis cerebri) of food animals, chiefly cattle. Ratio, 1:5. (The anterior lobe represents approximately 90 per cent. of the total gland.)

Active Principle: Tethelin. This substance, announced by Brailsford Robertson in 1916, is the growth-stimulating hormone from the glandular portion of the pituitary and is capable of increasing growth, especially of bones, and of hastening maturity experimentally in animals.

Standardization: Not yet satisfactorily standardized.

Relations: Cooperates with thyroid, gonads, and possibly adrenal cortex.

Harrower Products: Uniglandular—Pituitary (Anterior) from ½ to 5 gr. t.i.d.

Pluriglandular—(a) Antero-Pituitary Co. (tablets and solution) for use in the treatment of developmentally defective children, epilepsy, and growth dystrophies involving the pituitary (Frőhlich's syndrome).

> *Formula:* Pituitary (anterior lobe) gr. 2, Thymocrin gr. 1, Endothyrin gr. 1/12 with Calcium Phosphorus Co. q.s. ad. gr. v. ℞ Antero-Pituitary Co. (Harrower). No. C. Sig. *1, twice a day at meals, for four out of every five weeks.* Continue for several months. (In children past 8 years, and later in the treatment, 1, t.i.d.

(b) Pituitary Co. (tablets) in essential pituitary disease, especially pituitary obesity.

> *Formula:* Pituitary (total), Pituitary (anterior lobe) āā gr. 1½, with Calcium Phosphorus Co. q.s. ad. gr. v. ℞ Pituitary Co. (Harrower). No. C. Sig. *1, q.i.d., a.c.*

(c) Gonad-Ovarian Co. (tablets) in dysovarism where the well-known thyro-ovarian formula is used (see page 98), but where the condition is more resistant in character *and has a more definite pituitary factor.*

Formula: Thyro-Ovarian Co. gr. 3, Spermin Extract and Pituitary (ant.) āā gr. 1½. ℞ Gonad-Ovarian Co. (Harrower). No. C. Sig. *1, t.i.d., a.c.* If the patient is menstruating or if there is a molimen, prescribe as No. 4, *i.e.*, 1, t.i.d., a.c., for fourteen days; double dose from seven to ten days before menses (or molimen); omit for a week at onset of menses; repeat.

Explanation: These various products, the activity of which depends largely on their content of anterior pituitary substance and which are indicated in rather widely differing circumstances already enumerated, are given with the expectation of accomplishing two things: First, the replacement of some of the material properly produced by the anterior pituitary gland and which for some reason has become deficient; and, second, the encouragement (as a catalytic substance) of a more active function on the part of the pituitary and the reestablishment of its hormone-producing capacity as well as its influence upon the associated endocrine glands.

Hypopituitarism has a very wide range of clinical symptoms because of the fact that the anterior lobe of the pituitary is intimately associated with other endocrine glands, notably the thyroid and the sex glands. A pituitary disturbance, therefore, promptly becomes a pluriglandular problem with manifestations depending upon the extent of the loss of hormone production, the resilience or responsiveness of the dependent or associated glands, and, particularly, the time of life during which the endocrine change has been brought about (note the tables on pages 69, 70).

Suffice it to say that in defective children thyroid and thymus have been found of cooperative advantage, and the formula, Antero-Pituitary Co. (Harrower), is preferable to pituitary substance or thyroid alone. In gonad insufficiencies of both sexes, anterior pituitary sometimes is the one factor that has the greatest influence in the reestablishment of the functions involved, and many cases of dysovarism fail to respond satisfactorily to organotherapy and even to pluriglandular therapy with ovary, corpus luteum, or thyroid, or combinations of these, until the pituitary factor is added.

Contraindications: Hyperpituitarism.

B. Pituitary Total

Source: Same as Pituitary, Anterior Lobe. Ratio, similar.

Active Principle: None differentiated. Total pituitary substance is used for virtually the same purposes as anterior lobe substance, and to all intents and purposes is identical. The posterior lobe, representing less than 10 per cent. by weight of the total pituitary material, is removed for the preparation of Liquor Pituitarii leaving behind the anterior lobe which, in the writer's opinion, is practically of equal therapeutic value with the total substance.

Standardization: None.

Relations: Same as above.

Harrower Products: Uniglandular—Pituitary, Whole (tablets), from ½ to 3 gr. t.i.d.

Pluriglandular—Pituitary Co. (tablets). See (b) on page 103.

Explanation: There is virtually no difference in possibilities or effectiveness from anterior lobe, although with this opinion there will be several who will differ. The preparation, Pituitary Co. (Harrower), is a whole pituitary product, the essential endocrine or glandular part of which has been reenforced by the addition of an equal amount of anterior pituitary. Incidentally, the dosage (1½ gr. of each desiccation) is very much higher than that to which many physicians are accustomed. (This represents nearly 20 gr. of fresh gland, or 10 of the 2-gr. tablets, dosed on a fresh-gland basis.)

Contraindications: Late pregnancy.

C. Pituitary Posterior

Source: The minute posterior lobe of the hypophysis cerebri of cattle. Ratio, 1:4.

Active Principle: Infundibulin, Pituitrin, Hypophysin. This substance, announced by Blair Bell in 1909, is the oxytocic infundibular or posterior-pituitary principle capable of bringing about marked muscular contractions in the uterus at labor, and, in fact, in all unstriped muscle. It is an excellent stimulant of renal function as well as of mam-

mary activity, and seems also to favor carbohydrate metabolism. It is one of the most remarkable of the organotherapeutic extracts, and its physiologic action is effective in a widely varying range of clinical cases.

Standardization: By determining the response of the isolated uterine muscle of the virgin guinea-pig recorded by the kymograph. The "international unit" represents the physiological activity of 0.5 mg. of the standard dry acetone extracted substance of the fresh posterior lobe (supplied by the U. S. Department of Agriculture).

Relations: Cooperates with adrenal medulla. Antagonizes pancreas.

Harrower Products: Uniglandular—Posterior Pituitary (tablets) from 1/20 to 1 gr. t.i.d. Liquor Pituitarii, Obstetrical (ampules of ½ or 1 cc.; 10 international units per cc.). Liquor Pituitarii, Surgical (ampules of ½ or 1 cc.; 20 international units per cc.).

Pluriglandular—Pituthymin Solution (see page 140).

Contraindications: Early stages of labor with undilated os. Dystocia, malposition, or obvious obstruction. Extreme hypertension.

13. THE PLACENTA

Source: Placentas from cows. Ratio, 1:6.5.

Active Principles: Placentin and Estrin (announced by Dodds in 1926). The former substance apparently is not a hormone, but it exerts a marked therapeutic effect in bringing about an increased immunity to placental proteins, especially in cases of vomiting and nausea of pregnancy. It is also one of the most active galactagogues known. The latter, known as Plestrin, on the other hand, is the estrus-producing hormone that originates in the ovaries and is stored up in the placenta during that period when ovarian activity is in abeyance, *i.e.*, during pregnancy.

Standardization: By exactly the same method used to standardize Folliculin (see page 119) with identical results.

Relations: Cooperates with mammæ. Antagonizes corpora lutea.

Harrower Products: Uniglandular—Placenta Substance (tablets) from 2 to 5 gr. t.i.d. Plestrin Solution (ampules of 1 cc. each containing 25 Doisy rat-units).

Pluriglandular—(a) Placento-Mammary Co. (tablets) for use as a galactagogue and a uterine involutant (see under Mammæ, page 96).

(b) Placenta Co. (tablets), for use in reestablishing immunity to the placental proteins, especially in vomiting and nausea of pregnancy.

Formula: Placenta Parenchyma gr. 5, Endothyrin gr. 1/24, Calcium Phosphorus Co. q.s. ℞ Placenta Co. (Harrower). No. C. Sig. *2 sanitablets with charged or ice-water, q.i.d.*

(c) Sol. Placento-Luteum Co. for use in certain rarer types of vomiting of pregnancy (see under Corpus Luteum, page 88).

Explanation: The placenta is coming to be known as one of the most important sources of organotherapeutic products. The discovery that Plestrin, the placental estrin, which is capable of accurate physiologic standardization and of bringing about estrus in ovariectomized rats, is a more satisfactory product than that obtained from either the follicular fluid or the ovaries, has aroused renewed interest in the placenta. This comparatively recent development has in no way lessened the value of placental organotherapy in pregnancy (as a means of increasing the immunity to the placental proteins) or in postpartum circumstances (as a galactagogue and uterine involutant). Placentin, or the unstandardized placental fraction, is the most active galactagogue known, and its combination with mammary substance as in Placento-Mammary Co. (Harrower) —see under Mammæ, page 96—makes a postpartum remedy of decided advantage.

Note: More recently an unusually active placental concentrate (1:20) has been prepared especially for certain gynecologists who have been interested in developing a means of controlling the tendency to abortion. While it is too early to give definite reports, the early results have been unexpectedly good. (See page 141.)

Contraindications: None.

14. THE PROSTATE

Source: The prostate glands of cattle and horses. Ratio, 1:6.

Active Principle: Not known. The prostate, however, has an endocrine function, which was first properly emphasized in 1907 by Serralach and Pares.

Standardization: None.

Relations: Cooperates with gonads, thyroid, anterior pituitary.

Harrower Products: Uniglandular—Prostate Substance (total), from 5 to 10 gr. t.i.d.

Pluriglandular—(a) Prostate Co. (tablets) for use in simple prostatic hypertrophy.

> *Formula:* Prostate and Spermin Extract (Leydig cells), āā gr. 2, Nucleic Acid gr. ¼, with Calcium Phosphorus Co. q.s. ad. gr. vi. ℞ Prostate Co. (Harrower). No. C. Sig. *1, q.i.d., a.c.* (Occasionally, increases in this dosage are helpful.) Advisable to continue this form of organotherapy for several months.

(b) Gonad Co. (tablets and solution). See under Testes, page 110.

Explanation: The explanation usually given for the many excellent but empirical experiences with this measure, is that the prostate supplements the Leydig-cell endocrine functions, and when these begin to wane the prostate undergoes a gradual compensatory hypertrophy. These conditions are lessened by prostate therapy, apparently in the same way that compensatory enlargements of the thyroid or pituitary respond to the suitable organotherapy.

Contraindications: Prostatitis, chronic posterior urethritis.

15. THE SPLEEN

Source: The splenic parenchyma from calves, sheep, and other young animals. Ratio, 1:4.5.

Active Principle: Colloidogenin (?). This substance, announced by Dr. Charles Bayle in 1910, is believed to exert an influence upon the maintenance of the colloidal character of the mineral substances in the organism, which is

believed to be deficient in certain protracted infections, notably tuberculosis, where its absence permits of the loss to the organism of many of the essential mineral elements (demineralization), while, on the other hand, its replacement facilitates remineralization.

Standardization: Not yet standardized.

Relations: Cooperates with parathyroids and liver.

Harrower Products: Uniglandular—Splenocrin, tablets, 5 gr. t.i.d. Splenocrin Solution.

Pluriglandular—(a) Para-Spleen Co. (tablets and solution). See under Parathyroids, page 101.

(b) Hepato-Splenic Co. (tablets). See under Liver, page 92.

Explanation: The spleen is a mysterious organ, and there is as much difference of opinion regarding its organotherapeutic possibilities as there is about its physiology. Spleen extract is a hematinic. It is claimed also to exert an effect upon nutrition, especially in tuberculosis, paludism, and certain diseases of the spleen such as splenomegaly and splenic cirrhosis. Apparently, the mineral-regulating effect first emphasized by Bayle (briefly referred to above), is responsible for a part of its therapeutic possibilities. In our own work with the parathyroid active principle it was found that the spleen solution with which we happened to be working simultaneously also exerted a stimulating effect upon the blood-calcium index; but this effect, while more marked than that of parathyroid, was very fleeting, lasting only for a few hours. Many clinical experiences have confirmed the impression that spleen reenforces or supplements the therapeutic possibilities of parathyroid therapy and that there is a decided advantage in giving them together, as with Para-Spleen Co. mentioned above and on page 101.

Contraindications: None.

16. THE TESTES

Source: The testes of rams or bulls. Ratio, 1:7. (There is, however, an advantage in using the endocrine cells, or the interstitial cells of Leydig. Ratio, 1:10.)

Active Principle: Lydin. This substance, originated in our own laboratories in 1925, apparently is the essential Leydig endocrine principle containing the chemical substance known as Spermin. It has a marked gonado-stimulating, dynamic effect, but as yet is incapable of standardization, as is the case with its physiological counterpart, Plestrin (see pages 107, 119, and 133).

Standardization: Not yet physiologically standardized.

Relations: Cooperates with thyroid, anterior pituitary, adrenal cortex. Antagonizes thymus.

Harrower Products: Uniglandular—Leydig cells (desiccated) from 1 to 5 gr. t.i.d. Lydin (orchic solution).

Pluriglandular—(a) Gonad Co. (tablets and solution) for use in impotence, presenility, and hypogonadism.

Formula: Adrenal (total) gr. ¼, Endothyrin gr. 1/12, Pituitary (ant. lobe) gr. 1, Prostate and Spermin Extracts āā gr. 1½, Calcium Phosphorus Co. q.s. ad. gr. vi. ℞ Gonad Co. (Harrower). No. C. Sig. *1, q.i.d., a.c.* Note: From 3 to 8 sanitablets may be given daily.

(b) Leydig Cell Co. (tablets). This product is not now generally distributed, as it is used by only a few special workers. It is replaced by Lydin, on the one hand, and by Gonad Co. on the other (see above).

Formula: Spermin Extract (from Leydig cells) gr. 2½, Endothyrin gr. 1/16, Calcium Glycerophosphate and Calcium Phosphorus Co., āā q.s. ad. gr. v. ℞ Leydig Cell Co. (Harrower). No. C. Sig. *1, q.i.d., a.c.*

Explanation: The therapeutic possibilities of testicular preparations were first emphasized in a scientific way by Brown-Séquard in 1889 and, despite the reputation of this worker as a physiologist, this announcement gave organotherapy as a whole "a black eye." Undoubtedly this was because the suggestions of Brown-Séquard were taken up with avidity by the charlatans, and ridiculous claims and spectacular advertising seriously hurt what has since been developed into a respectable and effective form of therapy. Suffice it to say that an active principle may be obtained from the essential endocrine cells of the testes (the interstitial cells of Leydig), which exerts a marked gonad-stimulating effect and also a muscular and cellular

effect that was first demonstrated scientifically by means of Mosso's ergograph.

In asexualism, impotence, and functional presenility, however, one rarely finds true uncomplicated hypogonadism. This, of course, is more marked in the organic cases, especially of hypopituitarism (Frőhlich's syndrome), and in eunuchoidism where the anterior pituitary is most decidedly involved with the Leydig cells. Clinical experiences also show that the thyroid is concerned in the establishment of gonad endocrine function in both the male and the female. Therefore, while Lydin is an active gonad principle of distinct therapeutic worth and is used by many physicians, Gonad Co. (Harrower) which, as has been seen, is a combination of the Leydig cells (containing Lydin) with anterior pituitary, thyroid, and adrenal cortex, is a broader and more generally efficacious remedy, especially where there is general endocrine depletion. As this complication is inevitable in all senile and presenile cases, a more ideal treatment consists in administering this formula by intramuscular injection daily or every other day for a month or six weeks, and at the same time giving tablets of Gonad Co. (Harrower) one at meals and at bedtime for several months. It may be an advantage to double this dose for a period to determine whether there is a broader tolerance.

Contraindications: Orchitis.

17. THE THYMUS

Source: The thymus glands of calves, particularly from "bob veal." Ratio, 1:6.5.

Active Principle: Thymin (?). This substance is not yet fully understood or appreciated nor, for that matter, is the thymus generally accepted as an endocrine gland. Nevertheless, it is coming to have a more important position in organotherapeutic practice (see page 138).

Standardization: None.

Relations: Cooperates with thyroid and parathyroids. Antagonizes gonads and pancreas.

Harrower Products: Uniglandular—Thymus Substance (total) from 5 to 10 gr. t.i.d. Thymocrin Solution,

each cc. of which represents 4 per cent. of the essential thymus nucleoprotein, is used chiefly in psoriasis (see page 139).

Pluriglandular—(a) Thymus-Spermin Co. (tablets), for use in certain cases of "metabolic arthritis" where the cellular chemistry is defective.

Formula: Adreno-Spermin Co. and Thymocrin āā gr. 3. ℞ Thymus-Spermin Co. (Harrower). No. C. Sig. *1, q.i.d., p.c.* (Occasionally given in larger doses for a few weeks, then reduced to above.)

(b) Antero-Pituitary Co. (see under Pituitary, page 103) for use in developmentally defective children and certain cases of epilepsy.

(c) Pituthymin Solution (see under Pituitary, Posterior, page 106 and also pages 139, 140).

Explanation: The thymus gland is the original source of nucleic acid and, although sodium nucleate is no longer made from it, it is none the less a definite and decidedly active remedy. It has an effect upon the production and character of the blood, and for years has been recommended particularly as a leukocytogenetic. More recently (1927) it has been used to supplement and broaden the value of the hemopoietic liver fraction (see under Liver, page 94 and also page 131).

Thymus also exerts an influence upon the growth and nutrition, especially before 7 years of age when the thymus is believed normally to atrophy and disappear. For this reason it has been used as an integral part of the formula, Antero-Pituitary Co. (Harrower), which has been used very successfully in the treatment of developmentally defective children.

Thymus also appears to exert a real but entirely unexplained balancing effect upon the oxytocic influence of the posterior pituitary principle, making possible its safe administration in labor considerably earlier than has been thought proper with the posterior principle alone. Pituthymin (see page 140) apparently has made possible a decided improvement in the use of the posterior pituitary principle in obstetrical practice.

Contraindications: None.

18. THE THYROID

Source: The thyroid glands of sheep and, more recently, of all food animals. Ratio, 1:5.5.

Active Principle: Thyroxin, announced by Kendall in 1919. This is the metabolism-regulating hormone which is now available in definite chemical form and even capable of synthesis. There is at least one more important thyroid active principle to which attention has been called by Reid Hunt, Oswald, and others.

Standardization: Thyroid Extract is standardized to contain a certain definite amount of inorganic iodine—0.2 per cent. in the U.S.P. X.

Relations: Cooperates with adrenals (cortex), gonads, pituitary (anterior), and thymus. Antagonizes parathyroids (?) and adrenals (medulla) (?).

Harrower Products: Uniglandular—Thyroid Extract U.S.P., from 1/10 to 1 gr. t.i.d. Endothyrin (tablets and solution), ½ gr. or less b.i.d. Thyroid Co. (with remineralizing salts).

> *Formula:* Each sanitablet contains 5 gr. of Calcium Phosphorus Co. (see formula No. 11) with ¼ or ½ gr. of desiccated and standardized U.S.P. Thyroid. ℞ Thyroid Co. (Harrower) gr. ¼ or ½, as desired. No. C. Sig. *1 sanitablet t.i.d.*

Pluriglandular—(a) Adreno-Spermin Co. in asthenic, run-down conditions (see under Adrenals, page 86).

(b) Antero-Pituitary Co. in developmentally defective children (see under Pituitary, Anterior, page 103).

(c) Thyro-Ovarian Co. in dysovarism, menopause, etc. (see under Ovary, page 97).

(d) Iodized Thyroid Co. (tablets and solution) for use in goiter and hypothyroidism.

> *Formula:* Endothyrin, Ferrous Iodide, Nucleic Acid (Nuclein), āā ¼ gr. with Calcium Phosphorus Co. q.s. ℞ Iodized Thyroid Co. (Harrower). No. C. Sig. *1, t.i.d. between meals, with water.* (Occasionally it may be best to give from 4 to 6 sanitablets a day.)

(e) Thyro-Pancreas Co. with Ovary (see under Pancreas, page 100).

(f) Gonad Co. in impotence, asexualism, hypogonadism (see under Testes, page 110).

Explanation: The thyroid has well been named the "keystone of the endocrine arch." It is involved intimately with the functions of the other endocrine glands; is particularly influenced by toxemias; is a vital part of the immunizing mechanism; regulates the cellular chemistry, growth, and metabolism. Therefore, the indications for thyroid therapy are the most extended of all the endocrine remedies, and it is a valuable ingredient of a number of pluriglandular formulas. Because of this, it has been said that the only active substance in certain pluriglandular formulas is the thyroid, but with this, of course, we must differ. Suffice it to say that in asthenic, run-down conditions where the adrenals have been depleted, the toxemia responsible for the hypoadrenia depletes the thyroid also. Therefore, the formula mentioned above (a) contains a suitable dose of thyroid in addition to the adrenal substance.

Again, for many years it has been known that, of all the endocrine products, thyroid extract is the most likely to be useful in the developmentally defective child. It has been shown, however, that the pituitary and the thymus also play an important part. Therefore, in the formula (b) mentioned on page 113, the thyroid is supplemented by a large dose of anterior pituitary substance, also by thymus, the therapeutic influence of which broadens its value.

Attention has been called elsewhere (see pages 16, 17) to the importance of the thyroid aspect of dysovarism, particularly in the menopause. Ovarian irregularities are attributable to thyroid disorders as much as to ovarian or pituitary dysfunction. Therefore, in the thyro-ovarian formula (c) the thyroid ingredient is of particular importance—in some instances even more so than the ovary.

Wherever cellular chemistry is deficient, the basal metabolism low, and toxemia is interfering with the functions of the body in general, it may be expected that the thyroid is defective. This is particularly true in women at the menopause who have high blood-pressure. The formula (e) contains thyroid for this purpose. For the same reason it is an ingredient of the formula for impotence (f).

The two preparations, Thyroid Co. and Iodized Thyroid Co., are used in place of ordinary thyroid extracts in true hypothyroidism, as in cases of simple goiter. The advantage claimed for these formulas is that the excipient is a remineralizing, alkalinizing preparation calculated to lessen a part of the cellular chemical imbalance that the slowed thyroid function has brought about. On the other hand, the Iodized Thyroid Co. is prepared especially with the treatment of simple goiter in mind. This is not only a form of thyroid insufficiency but also a manifestation of iodine starvation. The nucleic acid has been added to the thyroid and iodine on purely empirical grounds, because it has seemed in many instances to make them both more effective. This formula is a specific for simple goiter.

Endothyrin is a total thyroid extract containing a larger proportion of the active principles because a greater amount of inert cellular dèbris has been removed. (The inertness of this material is demonstrated before it is discarded.) Judged by the U.S.P. X standardization, it is twice as active as Thyroid U.S.P., for it contains a minimum of 0.4 per cent. of iodine in organic combination. Endothyrin Solution apparently is coming into vogue. It contains 125 times more iodine per cc. than the next most active thyroid protein solution at present available.

Contraindications: Hyperthyroidism, Graves' disease.

HARROWER DISTRIBUTION

LEADING jobbers carry a full line of the Harrower preparations. They are secured from the following Branch Offices: *Atlanta,* 716 Hurt Bldg.; *Baltimore,* 1003 Lexington Bldg.; *Boston,* 46 Cornhill; *Dallas,* 833 Allen Bldg.; *Chicago,* 160 N. La Salle St.; *Kansas City, Mo.,* 329 Rialto Bldg.; *New York,* 9-11 Park Place; *Portland, Ore.,* 316 Pittock Block.

Following are the addresses of the Foreign Depots: *Australia,* 36-40 Chalmers St., Sydney; *Canada,* 172 John St., Toronto, 2; *England,* Rickmansworth Road, Watford, Herts.; *India,* The Endocrine Laboratory, Simla; *New Zealand,* G. P. O. Box 210, Christchurch; *South Africa,* 15 Bree St., Cape Town.

XII

STANDARD ENDOCRINE UNITS

The International (Post-Pituitary) Unit—The Collip and Hanson Parathyroid Units—Insulin Unitage—The Anabolin (Liver) Unit—Sato's "Rabbit Ammonia Unit"—Folliculin: Rat-Units and Mouse-Units.

IN ORDER TO facilitate an expression of the various strengths of endocrine solutions and to indicate the standards whereby the endocrine principles are evaluated, the term "unit" has been selected and in different instances has been given an arbitrary value, depending upon the product with which it is connected and the worker responsible for it.

Like various other units of measurement, such as inches, pounds, or gallons, endocrine units are purely arbitrary in character and, therefore, one must memorize the various methods and standards that have been used in their determination. It has seemed advisable to collate here a list of the units of standardization used in endocrinology, a thing which the writer has failed to find in any other publication.

As will have been found elsewhere in this book, several endocrine principles are standardized in a chemical fashion, notably thyroid (page 113) and adrenal medulla (page 87). Others are standardized by adhering to certain gravimetric procedures in the course of their manufacture, like Hemopoietin (page 94), Ovarian Extract (page 97), and Lydin (page 110), while the remainder constitute a group of substances capable of accurate physiologic standardization. These latter include the principles from the posterior lobe of the pituitary, the parathyroids, the

islands of Langerhans, the liver, and the ovaries (and placenta). These "standard endocrine units" are explained below.

Posterior Pituitary. The so-called "international unit" (I. U.) is a kymographic measurement of the response of an isolated uterus from a virgin guinea-pig to the physiological influence of the preparation. The United States Department of Agriculture will supply the so-called "standard dry acetone extracted substance of the fresh posterior lobe," which is used as the "known," and an international unit represents a physiological activity corresponding to that of 0.5 mg. of this standard product. (See page 106.)

Parathyroid. The parathyroid hormone exerts a decided, uniform, and measurable influence upon the blood calcium. The measure of its activity is studied in two ways: The Collip method and the Hanson method. While Hanson was the first to standardize parathyroid extract, Collip was first to emphasize a method of standardization and to bring his measure down to a basis of "units." The Collip unit, therefore, is better known than the Hanson unit.

A Collip parathyroid unit is one one-hundredth of the amount of the parathyroid active principle required to raise the average blood-serum calcium in normal dogs of known weight (20 Kg.) by 5 mg. within fifteen hours.

On the other hand, Hanson prefers to standardize the parathyroid hormone on parathyroidectomized dogs. Within twenty-four hours after this operation, the blood-serum calcium falls about 30 per cent. An injection of the original Hanson HCl-X extract equivalent to 0.3 Gm. of fresh true parathyroid tissue will restore this deficiency to normal within six hours. A Hanson parathyroid unit, then, is one one-hundredth of the amount of extract required to produce each milligram of rise in blood calcium in dogs of uniform weight under the abnormal conditions stated.

Pancreas. The standardization of the Langerhansian hormone, commonly known as insulin, is accomplished by studying the influence of injections of known amounts upon the blood sugar of animals.

The original unit of Macleod was the amount of insulin required to reduce the blood-sugar index of a 2-Kg. rabbit 0.045 per cent., producing hypoglycemic convulsions within from two to five hours. This unit being considered too large, a clinical unit of one-third the amount mentioned above was adopted later.

Liver. Very considerable interest has attached to the perfection of "the detoxicating hormone of the liver." The original finished product, known as Anabolin, is standardized by measuring (by means of the kymograph) the blood-pressure variations in a normal dog. One cc. of a "standard solution" of Anabolin is capable of reducing the blood-pressure of a 10-Kg. dog by 12 points. A concentrated solution is also available, 1 cc. of which will reduce the blood-pressure in a dog of the same size by 25 points. In order to make comparisons between Anabolin and the more recent liver extracts, the term "unit" has been used. This is the amount of liver extract required to reduce the systolic blood-pressure of a 10-Kg. dog by 1 mm. of mercury. Hence the standard 1-cc. dose of Anabolin contains 12 units.

The Japanese investigator, Prof. Akiro Sato, has developed a means of quantitative study of detoxication by the liver and its modification by "the detoxicating hormone of the liver," as he calls it. He administers one of a series of poisons with known toxicity (such as a fresh 3 per cent. ammonium chloride solution) and, by judging the influence of these products upon a large number of animals, he determines the amount that will produce convulsions in a rabbit of given weight within fifteen minutes. He has found it possible with his liver preparation to nullify this toxic effect and to abort these convulsions. (See page 129.) In order to set down his quantitative estimations, he has used as an arbitrary figure what he calls a "rabbit ammonia unit" (R. A. U.). Such a unit, therefore, is a measure of the hepatic detoxicating power based upon the weight of the rabbit, the amount of known poison used to bring about convulsions, and the quantity of liver extract capable of preventing these convulsions in the manner outlined by Sato.

The Female Sex Hormone. Since the epoch-making studies of Doisy and his associates at St. Louis University, it has been found possible to separate the active, estrus-producing principle, or essential female sex hormone. As has been stated elsewhere (page 133), it was separated from the fluid in the graafian follicles, later from whole ovarian substance, and still more recently from the placenta. This follicular hormone or estrin is standardized in "rat-units," one of which represents the amount of this principle required to induce estrus within three days in a sexually mature, ovariectomized rat weighing approximately 140 Gm. Estrus is determined by the microscopic smear method.

In Holland and Germany a considerably less active substance has been used than in America, and almost all the papers refer to *Mauseeinheit* (abbreviated "M. E."). A mouse-unit is apparently one-quarter of a standard rat-unit.

HARROWER ORIGINALITY

IT is not easy to originate, and, without a doubt, many of the ideas associated most definitely with the Harrower name and products are not absolutely original with The Harrower Laboratory. Nevertheless, "the pluriglandular idea" is definitely connected with this organization, and much criticism has come from sponsoring it so extensively and intensively to the profession in the English-speaking countries. This, however, is now in the past, for *the pluriglandular idea is admitted to be scientific.*

Time and again, Dr. Harrower has credited the two chief pluriglandular ideas represented by Adreno-Spermin Co. (Harrower), on the one hand, and by Thyro-Ovarian Co. (Harrower), on the other, to French physicians who, years ahead of us in this country, have for decades been using organotherapy and pluriglandular therapy with success. However, many methods of perfection, manufacture, and standardization are original with this organization.

Besides this, a number of original products which The Harrower Laboratory was the first to perfect and make available to the medical profession are listed in the "Ready Reference List of Endocrine Remedies" (sent to any interested physician on request). Among these are Anabolin and Plestrin in their present stable and active form.

APPENDIX

A. HOW I HANDLE AN ENDOCRINE CASE

IN VIEW OF all the data gathered together and set down in the body of this little book, a story such as this may seem superfluous. But it has been especially requested, and no great harm can come from disclosing my usual routine to those who may care to read it.

First, it must be admitted that most of the cases that I see are second-hand, that is, they are referred, problem cases, and are supposed to have been classified previously as endocrine in character. Nevertheless, the routine is the same:

Objective Manifestations—While living several years in New York City, I acquired the habit of making "the subway diagnosis"—a shrewd guess about the individuals sitting opposite me, based solely on what I could see—the facies, the skin, the build, the eyes, the teeth, and the *tout ensemble.** It is surprising how much endocrine diagnostic help one can get from such a study. The eyes give us much information about thyroid function (hypo- or hyper-). The skin is a mirror of the endocrine chemistry—in many cases at least. (The chief endocrine gland is so intimate with the skin that its most common disorder, myxedema, very obviously involves the skin.) The shape of the face, too, the spread of the eyes and even the character of the eyebrows, the teeth and their juxtaposition, yes, and the size of the lower jaw, all tell their endocrine story.

*The following endocrine disorders can be diagnosed with fair accuracy by observation alone: Myxedema, cretinism, Graves' disease, acromegaly, eunuchoidism, Frőhlich's syndrome, Addison's disease, hypoparathyroidism (tetany, Parkinson's disease).

Naturally, then, I make this "subway diagnosis" unconsciously while the patient is greeting me. Then, having made my own unspoken snap-diagnosis, I proceed to see how far off I am—or if I am right!

Clinical History—The history of an endocrine case is quite like the ordinary anamnesis and, in view of the hereditary nature of some endocrine troubles (especially goiter and dysovarism), I always ask about such things, not only in the parents and grandparents but also in the aunts and nieces. The geographic aspect of the case is important too, for goiter (and the reactions to it by other endocrines) is often a matter of location. (So is alimentary parasitosis—see later.)

Foci of Toxemia—Since, as we have seen, toxemia is the outstanding cause of endocrine dysfunction, it is not long before I am busily uncovering every kind of toxemia. Usually I begin with the head and work down —teeth, tonsils, sinuses, gall-bladder, bowels, appendix, colon, pelvis (prostate or uterus), and, for that matter, any foci of infection discoverable. It is surprising how many leads to trouble one can find in the alimentary tract; in fact, I should judge that three-fourths of all the functional endocrine syndromes either originate in or are aggravated by some alimentary difficulty. Let us analyze these focal troubles, considering them in the same order that we have thus far:

Teeth—Carious teeth, poorly spaced teeth, and orthodontic irregularities, pyorrhea, and subdental abscesses (dental radiography virtually an essential in this work) —all are factors, actual or contributory. I have seen case after case of serious endocrine dysfunction, many of them with hyperthyroidism ready for operation, dependent almost wholly upon mouth conditions.

Tonsils—Always consider them; always verify the statement that "they have been removed"; always remove them if they are bad. Tonsil infections are closely related to thyroid troubles, not only on general grounds but because of the close lymphatic connections.

Nose—Ask especially about hay-fever, asthma, etc.

Sinuses—Investigate, transilluminate, refer if necessary.

Digestion—Indigestion is a cause of toxemia, sympathetic imbalance, and malnutrition—all of them important endocrine derangers. I have in mind a case of ovarian indigestion, which even one of the best-known gastro-enterologists did not connect with its real cause and consequently he treated it unsuccessfully. A colleague read a book of mine, noted something in it about dysovarism and the sympathetic, and the sympathetic and digestion, and promptly cured the girl (with Adreno-Ovarian Co.—Harrower—by the way).

Alimentary Toxemias, infections (bacterial), and infestations (protozoal) are among the most common disturbers of endocrine harmony. Even if they are not actually the cause of the ailment, they very often aggravate it and should be considered in connection with our attempts to control the dyscrinism.

Defective Detoxication—Many a dyscrinism results from a breakdown in the capacity of the organism to handle poisons—chiefly the poisons produced in the body. The resulting poisoning disturbs the endocrines, overworking the thyroid, adrenals, and other detoxicating organs, and then depleting them.

Hepatic Insufficiency looms large to me, for hepatic detoxicative defects are most common and important. Besides, I am always on the lookout for an excuse to use Anabolin and to confirm my present knowledge about it. Several hepatic function studies are intriguing. Biliary insufficiency is equally important, for it may interfere with the jejuno-ileal functions, underlie gallstones, cholecystitis, and even mucous colitis—all of which may be foundation stones in the building up of endocrine complexes, including, by the way, diabetes.

Here I find out about allergy, anaphylaxis, or protein sensitization. Many patients are eating foods that are actually poisons *to them,* or they are drinking coffee, unmindful of its endocrine irritating effect. Asthma, hay-fever, and other evidences of protein sensitization explain sensitiveness on the part of other endocrine

organs. This may be a serious hereditary feature or it may be of minor importance—*but it is a factor none the less.* If necessary, later, I extend the studies by a complete series of protein sensitization tests and a study of the stools (for six days in succession), for one can have allergy as a result of intestinal parasitosis or infection. A subtle overlooked toxemia is often the cause of an endocrine diagnostic failure!

Laboratory Tests—The extent of the study of toxemia reaches to several ordinary laboratory tests: (1) the urinalysis (twenty-four-hour specimen), looking out especially for acidity, indican,* and all the usual things; (2) the blood findings, including particularly the differential white count (for lymphocytosis and eosinophilia are often endocrine findings), and anemia, like malnutrition, must *also* influence the endocrines. (3) The blood chemistry occasionally helps as does no other test. This is important in studying disorders of the arterial tension. Blood-sugar estimations in diabetes and hypopituitarism, and blood-calcium findings in parathyroid dysfunction are particularly helpful. (4) The renal efficiency test (phenolsulphonephthalein) is made to prevent mistakes in diagnosis and to avoid the danger of giving Anabolin in cases with nephrosclerosis. (See page 84.)

The Thyroid—So far, the study has been general in character. I then start to concentrate on the thyroid features. The appearance already has given a lead. Goiter has been seen; it is now carefully palpated. The softer, diffuse, colloid types usually are the less serious hypothyroid types; while the hard, nodular type is more likely to be adenomatous and more serious. Remember that goiter need not accompany either marked hypo- or hyperthyroidism.

The puffy, heavy, inactive type is often true hypo-

*Indican is an excellent indicator of hepatic detoxicative defects. True, it is due to alimentary toxemia caused by protein putrefaction, but the liver is supposed to destroy these poisons *including the indican.* Hence it reminds us of both of these defects. (See Chapter X.)

thyroidism. The skin is harsh, dry, and cracking; the hair is dry, and the nails are brittle. Headache is common, especially the dull, indefinite type that occurs in the morning. The patient is generally "achey" and may be rheumatic or neuralgic, the joints often "crack," the circulation is poor, "dead" fingers and cold hands and feet are common. Sluggishness is the rule—mental, cellular, and alimentary. Hence the symptoms range from loss of memory, or inability to concentrate, to constipation and ptosis.

Many complex disturbances are built upon dysthyroidism for, as Hertoghe once said, "No tissue is able to escape the results of impoverishment of the thyroid gland." This is true of the other endocrines also.

The Ovaries—Then comes the ovarian side—a common feature in this line of work, for two-thirds of the endocrine cases are women,* and *all* of them have some sort of functional irregularity related to the gonads, even supposing "the menstruation is all right so far as I know."

The history is especially important here, for a great many endocrine disturbances are based on a stressful experience at or before puberty. In fact, it is my opinion that a common cause of goiter in girls is the incidence of scarlet fever, influenza, or other infectious diseases at the time when the thyroid is supposed to be initiating the ovarian function. If there is much toxemia or if the patient is a poor "eliminator," the thyroid is strenuously occupied with three different things: The regulation of metabolism, the maintenance of the immunizing response, and the establishment of ovarian function. In many instances it fails to accomplish the task demanded of it, and the result is functional enlargement and a corresponding irregularity in the ovarian function. Serious diseases of all descriptions interfere with ovarian function through the related glands, particularly the thyroid and adrenals.

*Ninety per cent. of thyroid insufficiencies occur in women, and 95 per cent. of these appear in the decade between 40 and 50. Seventy per cent. of all hyperthyroid cases occur in women.

The history, therefore, will be made to develop these points if possible and to show where such disturbances were followed by marked ovarian irregularities.

Many problems are complicated by dysovarism—if not by the actual ovarian irregularity, then by the other endocrine reactions to the ovarian disorder. Among these may be mentioned neurasthenia, epilepsy, and certain dermatoses (acne, pruritus, etc.). The point in this endocrine investigation is to connect these conditions with the ovarian factor, and in this the periodicity of the ovarian hormone function helps us. Sometimes it is necessary to have the patient mark a calendar with the information desired so as to show the periodic relationship that may be suspected. This is especially important when there is but a molimen instead of proper menstruation.

The Adrenals—The study of previous toxic experiences may lead to a consideration of a functional adrenal depletion, and this is particularly interesting when the patient comes with a story of marked fatigability, lack of initiative, subnormal temperature, reduced circulatory efficiency, and low blood-pressure—a typical picture of functional hypoadrenia. Undoubtedly this condition is more frequent in individuals who have had serious stressful times in the past, and in whom the adrenals have been greatly overstimulated.

The serious infections and toxemias already referred to as interfering with thyroid function also influence the adrenals. (That is why the post-toxic picture of hypoadrenia, such as so commonly follows influenza, is *a thyro-adrenal complex* and is so satisfactorily treated with Adreno-Spermin Co.—Harrower.)

Too much stress cannot be laid on this vitally important phase of dyscrinism. The circulatory features, which usually are so prominent, have for years been much more appreciated in France. The syndrome that Martinet named "hyposphyxia" is a condition of circulatory semi-asphyxia with venous stasis, insufficient arteriolar circulation with cold extremities, and occasional slight blueness (often a mottled appearance)

of the skin on different parts of the body, especially the exposed parts. In such individuals the blood-pressure is usually very low (90 or 100 mm.), although it is quite true that extreme degrees of tension may cause a functional insufficiency of the adrenals by localized hemorrhage into the glands.

Urticaria and other severe vasomotor skin symptoms are among the well-marked findings in persistent hypo-sphyxia, while lesser degrees may cause flushings and sensations of passing distress localized in various areas of the skin. The adrenal origin of some forms of urticaria is seemingly confirmed by the occasional "miraculous" disappearance of large and most uncomfortable wheals following a single hypodermic injection of from 5 to 10 min. of Endophrin Solution.

The muscular and nervous manifestations also are important. Asthenia is the rule and muscular tone (both striped and unstriped) is poor. Exertion is virtually impossible, and the "fatigue syndrome" is prominent. The intestinal musculature is inactive. Stasis, a common cause of hypoadrenia, is also a result of it. According to Tom Williams, mental exertion, even the simplest, often causes so much weariness and exhaustion as to be prohibitive. Mental elasticity is lost and there are both mental and physical depression with the fear that the individuals cannot now accomplish their accustomed mental work, and the story that they "have lost their nerve." With this, one frequently notes a fear of making wrong decisions and a vacillating frame of mind. This is the most common form of adrenal insufficiency. It is chronic both in origin and in its course. The greatest single cause, as we have seen, is chronic toxemia either of alimentary or focal infective origin. Fortunately the control of the cause and suitable "adrenal support" are followed by very encouraging results.

The Pituitary—There still remains one more "principal ductless gland" to consider—the pituitary body. The study of the pituitary features of the case before us involves the changes in the appearance already re-

ferred to (and outlined carefully in the charts on pages 69, 70). One looks especially for the peculiar type of obesity (girdle type), the modifications of gonad function, as well as somnolence and the quite common pituitary headache. When the latter is marked, one should not fail to investigate the vision, looking for bitemporal hemianopsia and other evidences of the pressure due to a pituitary tumor. Whether conditions are advanced to this stage or not, a radiographic study of the sella turcica is made and a sugar-tolerance test run in all cases with evidences of pituitary dysfunction.

By the time all the foregoing investigations have been made, quite a mass of evidence has accumulated to supplement the original "snap diagnosis," and in many cases a complex series of disturbances is pointed out for which recommendations are made immediately. All the various tests and signs already referred to (in Chapter X) are helpful, the various signs being noted in the objective study and the later diagnosis, while the laboratory procedures, general (urine, blood, etc.) and specific (B.M.R., sugar tolerance, etc.), confirm or upset our conclusions.

Diagnostic Treatment—The treatment of complex endocrine problems consists chiefly in the control of the numerous factors outlined here which are interfering with the normal function of these glands. While these factors are being controlled (if this is possible), the indicated organotherapy is prescribed and in many instances this may be done for therapeutic as well as for diagnostic purposes.

An analysis of these many points, bearing in mind the information collated elsewhere in this book, will afford a dependable diagnosis in probably 95 per cent. of the cases. The best thing I can say about endocrine insufficiencies is that, when they are discovered and the missing substances are replaced or the capacity to produce them is restored, the therapeutic response is quite the best confirmation of our diagnostic ability. In no other phase of medicine is this feature so marked.

B. THE NEWER POSSIBILITIES IN ORGANOTHERAPY

The Liver Hormones: (1) in Toxemias (2) in Anemias—The Female Sex Hormone in Sterility—The Parathyroid Hormone in Arthritis—Thymus Therapy: (1) in Psoriasis (2) with Post-Pituitary in Labor—Placental Extract in Threatened Abortion.

MANY OF THE therapeutic possibilities in this special field have been in use for years so are no longer novel.

The profession has become accustomed to the remarkable benefits that are expected from thyroid therapy (since 1891), from epinephrine (1901), from the posterior pituitary principle (1909), or from insulin (1922). Occasionally an idea crops up regarding the application of an old method or product in a new way and renews our interest in and appreciation of endocrinology. Hence our knowledge of the endocrine glands and their principles is being added to from year to year. Some of the newer possibilities of organotherapy, which are outlined here, are giving an entirely different aspect to this subject and creating new enthusiasm for it on all sides.

As Prof. J. J. Abel, of Johns Hopkins, said at the last meeting of the American Association for the Advancement of Science, in New York (December 27, 1928), "We are only at the beginning of knowledge concerning the chemical and physiological problems that are presented in this great field."

The Liver Hormones

The liver has been studied in quite a new fashion during the last five years. This has come about by the discovery of the detoxicating liver hormone (known as Anabolin) and, more recently, by the perfection of a hemopoietic fraction (known variously as hemopoietin and heparhemin). The results obtained by the administration of these preparations have been so spectacular as to awaken an interest in the whole subject on the part of many who heretofore have felt that there was a

suspicious element about organotherapy that made them avoid it. As a prominent Southern physician recently said, "We are becoming liver-minded." This great organ is now beginning to be looked upon in a very different light, for, in addition to its well-known production of bile, storage of glycogen, and detoxication, it has been decisively proved to be an important gland of internal secretion, producing at least two catalytic, hormone-like substances, which to many seem to act in the same way as do the internal secretory principles from other endocrine glands.

A Detoxicating Hormone—Since 1925 Anabolin, an active standardized soluble principle extracted from the liver by fractional methods, has been used largely as a means of reducing functional high blood-pressure. More recent experience indicates that Anabolin is not really a depressor principle, as was at first supposed, but that it exerts a direct stimulating effect upon the detoxicating function of the liver, hastening the destruction of certain waste products, like guanidine, that are pressor in character. Coincidentally, Anabolin increases the circulation in the liver, obviously stimulates its cellular chemistry, and also reduces the blood-pressure. This is used as a means of standardizing the product. If an increased tension is due to toxic causes that are permitted to reach the pressor mechanism through a breakdown on the part of the liver, such increases as we are able to make in hepatic detoxicating function naturally will reduce the blood-pressure, and the coincidental general betterment so commonly noted in hypertensive cases that are benefited by Anabolin, confirms the impression that various poisons previously allowed by the liver to enter the circulation are now being more properly disposed.

That hepatic detoxication is controlled by the liver principle, has been convincingly demonstrated by Sato, of Sendai, Japan, whose experiments on more than 1500 rabbits were reported in a series of five articles in 1927. He concludes that this hepatic principle "is capable of detoxicating any liver poison." Briefly, his method con-

sists in determining the capacity of rabbits to destroy certain poisons. The animals were classified according to their response to certain amounts of fresh 3 per cent. ammonium chloride solution which would cause convulsions within fifteen minutes in a rabbit of given weight. Knowing in advance the convulsive dose of ammonium chloride, a "protective" injection of the liver principle was administered just prior to the injection of the poison. The convulsions were prevented, and this detoxicating influence was demonstrated with remarkable uniformity. The same thing was done with several other substances, notably chloroform, histamine, and massive doses of urea.

Still further developments regarding the detoxicating influence of this hepatic principle were reported by Stoland, of the University of Kansas, at the last meeting of the American Medical Association (Minneapolis, May, 1928). He found that the tetanic manifestations in parathyroidectomized dogs also could be controlled with hepatic extract (as well as with the parathyroid active principle, as is well known). The controlling of the tetany, as Stoland puts it, evidently was brought about by a hastened detoxication or neutralization of toxic substances by the liver, since special attention was called to the fact that, following injections of the liver principle, the blood-calcium figure remained unchanged (whereas parathyroid injections apparently improve the tetany by raising the reduced blood-calcium figure).

Anabolin has been used also in the hypertension of late pregnancy and even in an occasional case of eclampsia, and the impression is gaining ground that this condition is the result of a breakdown in hepatic function which Anabolin is capable of modifying. At all events, many cases of preeclampsia have been improved and eclamptic convulsions controlled by Anabolin. Recently Miller and Martinez, of Pittsburgh, have reported an unusually good average of results from the use of liver extract in the toxemia of pregnancy in 255 preeclampsia cases.

One of the latest and rather remarkable developments with Anabolin concerns its broader usefulness. It has been found of value in toxic conditions *with low blood-pressure,* and undoubtedly the reason is that in both hyper- and hypotension the liver has been responsible for a toxemia which, on the one hand, has driven the blood-pressure-raising mechanism and, on the other, has depleted it. These experiences convince us that we have entered a new era in the study of hepatic function and therapy.

The Hemopoietic Principle—According to press reports, Dr. Morris Fishbein, Editor of the *Journal of the American Medical Association,* claims that the outstanding advance in medicine during 1927 was the successful treatment of pernicious anemia with liver diet and therapy. The work of Murphy, Minot, Cohn, and other investigators at Harvard University has crystallized for the profession some laboratory findings published as far back as 1920 by Whipple and his associates. Whipple showed that dogs, made anemic by repeated bleedings, improved more following liver feeding than any other hematinic measure. This idea was of only experimental interest until five or six years later when the startling reports and blood-counts of the Harvard workers began to be published. Since then, many scores of convincing papers have been published in all parts of the world. In the enthusiastic words of the conservative editor of the *Lancet* (London, April 28, 1928, p. 863): "The introduction of the Minot-Murphy treatment ranks as one of the most sensational episodes in the history of medicine. . . . Two years ago there would have been few medical men credulous enough to believe in the possibility of so simple and yet so specific a cure for a hopeless condition."

In addition to its other functions mentioned previously, the liver apparently is responsible for the regulation of at least a part of the hemopoietic mechanism. No definite proof as to how this comes about is yet available, but increasing emphasis is being placed upon the point that evidently the liver in some subtle catalytic way arouses or sets in motion the production of reticulocytes, and when this function is defective it may be

encouraged by feeding liver, which exerts "a true hormone action," as a prominent German writer puts it.

At first all the reports referred to the administration of liver diet or liver extract in the true, pernicious, or Addisonian type of anemia, and several statements cropped into the literature indicating that its value was limited to these cases. This, however, is not true, for hepatic hemopoietic hormonic stimulation is likely to be of value in any serious anemia, whether pernicious or secondary.

A great impetus to the application of hepatic therapy in non-pernicious types of anemia was given by an article in the *Journal of the American Medical Association* (Jan. 14, 1928, xc, p. 75) from the University of Oregon, telling of experiments with an extract of the liver rich in the nucleins, or sodium nucleate. Based upon this report, our own hepatic hemopoietic preparation (Heparhemin) was combined with large doses of sodium nucleate to form what is now known as Heparnucleate.

Heparnucleate is one of the best hematinic remedies at present known. In pernicious and serious secondary anemias (not, of course, in the simple anemias with a very slight reduction in the blood-count) it is capable of doubling or even of trebling the red-cell count.* An interesting factor has become increasingly evident in the clinical reports—"100,000 red cells per cu. mm. per day per dose." This is not an unusual result from the use of Heparnucleate and, as has been said, the worse the case, the better the results are likely to be.

Heparnucleate has been used in pernicious anemia with almost perfect results, yet I disagree with the Editor of the *Lancet* (quoted above) and believe that it is by no means a "cure." It has been used in the secondary anemia of alimentary parasitosis with wonderful changes in the blood findings. It has been used in post-hemorrhagic anemias with equal benefit, and time and again it has been used as a preoperative measure when the blood findings were too low to permit anesthesia with safety.

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*A report received February 18, 1929, from a Washington physician tells of another physician's father, age 59, with Hgb. 40 per cent. and r.b.c. 1,800,000, who took two tubes of Heparnucleate daily. Thirty days later the Hgb. was 95 per cent. and the r.b.c. 5,010,000!

Some interesting speculations have arisen following the consideration of these two important developments regarding the liver and liver therapy. Why are the serious anemias always associated with extensive alimentary toxemia and infection? Why is the hepatic detoxicating influence defective in serious anemia? Why should there not be some relation between these two important hepatic hormonic functions just as there is in other endocrine glands with dual activities (*e.g.*, the digestive and endocrine functions of the pancreas; the detoxicating and calcium regulating functions of the parathyroids; the pressor and musculotonic influences of the adrenals, etc.)? We are concerning ourselves at present with an attempt to uncover reasons for detoxicative breakdowns and to show what effect these toxemias have on the production of anemia, and *vice versa*.

The Female Sex Hormone

Ovarian therapy has come in for an unusual amount of consideration during the last few years, due largely to the perfection of an active estrus-producing principle, known as Folliculin. This is identical with the substance originally separated from the follicular fluid of the graafian follicles by Doisy and his associates at St. Louis University. This female sex hormone, or Folliculin, later was prepared from the entire ovary at a very great saving. Incidentally, Folliculin, made available to the profession by The Harrower Laboratory in June, 1926, was *the first* standardized ovarian preparation.

The most recent development with this substance has been the application in an extensive way of the idea, demonstrated by Dodds and his associates at the Middlesex Hospital Medical School, in London, that the estrus-producing hormone or estrin apparently is stored up in the placenta during pregnancy and may be found in that organ in far greater concentration than elsewhere. As a result of this we are now able to obtain a far more potent and less expensive product. It is known as Plestrin, the placental estrin, and now replaces the original Folliculin. It must be remembered that this substance actually is capable of bringing about estrus or rut *in ovariectomized*

animals and also of establishing estrus in immature animals. More recently it has been found that certain animals, past the stage of reproductive activity, have come into heat again following injections of this estrin and have carried one or more belated litters to term.

Plestrin is physiologically standardized and apparently is identical with Folliculin. It is obtainable in concentration five times greater (25 rat-units per cc. instead of 5) and at a unit price one-seventh that previously charged. It is essentially a trophic hormone, and it may be stated in passing that injections of Plestrin into small rabbits have caused hypertrophy of the entire sex mechanism—ovaries, tubes, uterus, and horns—amounting to as much as 1500 per cent. in six weeks (by actual weight). It should be mentioned, however, that no such spectacular hypertrophic influence has been noted in clinical practice!

Extensive experiences with Plestrin and with its predecessor, Folliculin, have demonstrated that its principal field of clinical usefulness is in the control of functional ovarian insufficiencies such as we expect in infantilism, amenorrhea, and, particularly, sterility. In fact, the greatest service that has been accomplished with Plestrin is in sterility. All the reports and communications confirm its superiority in this special field. For example:

"We have had some most gratifying results in patients in whom we had utilized every available and rational means of therapy at our command. Many of these patients had been under our care from two to four years and in a few cases longer. We have, I think, at least from twenty-four to thirty successful 'takes' from the use of Folliculin, and most of these have been those that did not respond to the other more common forms of therapy—douches, pessaries, tonics, gland preparations by mouth, dilatations, etc. I can recall seven or eight successful cases in the past month; these, of course, represent patients many of whom have been under our care from many months to three years or more.

"I do not care what others may say, I know personally that it is effective and that it has solved the problem of

a goodly number of our sterility patients where other factors were ruled out. Of course, we have failed in some cases, but all the time we are getting the desired result in some of the most resistant and puzzling problems.

"The action involved seems to be a combination of stimulation and stabilization of the reproductive system. We utilize other measures as indicated along with the Folliculin, and continue the injections three times a week until about three dozen have been taken before stopping for an interval of no treatment. There is very little if any menstrual change. In a few instances the periods have been lessened, or have been somewhat irregular, but in most of these pregnancy has occurred within a few weeks of this phenomenon. I can see no deleterious effects, but can report very hopeful results. In fact, the menstrual change mentioned above would seem to indicate an active response to the therapy in certain cases. We are now using Plestrin instead of Folliculin but in the same way."

It should be mentioned here that Plestrin has no effect upon the menopause and cannot be used as ordinary ovarian extracts or as the pluriglandular formula, Thyro-Ovarian Co. (Harrower). Obviously, its particular influence is not required at the change of life. When the normal waning of ovarian hormone function begins to take place, an abnormal activity on the part of the thyroid and the pituitary complicates an otherwise simple matter. If the change of life were nothing but an ovarian insufficiency, one would expect only a gradual waning and discontinuance of the ovarian functions; but too often it is a serious, stormy, uncomfortable experience resulting from difficulties in these other endocrine glands. Therefore, ovarian therapy alone cannot affect a complex condition like this, and naturally Plestrin would be altogether useless.

Plestrin is best given in a certain irregular fashion, there seeming to be an advantage in bunching the injections and pushing the dosage prior to the expected menstruation or molimen and then stopping for a brief pause after this has passed. Failure should not be admitted until at least 1000 rat-units have been given over a period of several months.

The Parathyroid Hormone

Some very fascinating developments have come about fairly recently regarding the parathyroid active principle. Because Adolph Hanson, of Minnesota, made possible the standardization of this preparation (his work being confirmed later by Collip, of Canada), this product has come in for a good deal of study and is now considered as having possibilities in therapy very much more extensive than were originally supposed.

It may be recalled that parathyroid extract was first used chiefly in the treatment of Parkinson's disease, and, it is still rendering a more useful service in this condition than has been noted from any other remedy. Later, as a result of the intensive work of Vines and Grove, in Cambridge University, the parathyroid principle was found to be capable of modifying an abnormal blood-calcium level. Parallel with this, its remarkable influence was made clear in the control of certain ulcerative states like leg ulcers, sinus infections, chronic otitis media, etc. Since then, Paracalcin (Harrower), Paroidin (Hanson), and Parathormone (Collip), as the standardized parathyroid active principle is variously called, have been found to be specific in the control of tetany, both clinical and experimental, and in certain calciprivic states related to hypoparathyroidism.

The parathyroid principle, then, modifies the calcium-fixing powers of the blood and may be used with advantage in hypocalcemia. As it also modifies the coagulability of the blood, evidently through its influence upon the blood calcium, it is now used quite frequently to prevent the hemorrhage that so often follows such operations as tonsillectomy; also in purpura and other hemorrhagic diatheses.

Several unexpected indications for this remedy have been mentioned, and are very intriguing. It is suggested that parathyroid has rendered decided service in such widely differing conditions as chorea and arthritis. In both these diseases, the benefit apparently is related to the calcium regulation. In the latter, particularly, the

inference is that the parathyroids may influence the ionic character of "calcium gone wrong." Since arthritis is so serious and hopeless a proposition, any suggestion that holds within it the slightest possibility of benefit should receive consideration. Here are some suggestions regarding the present possibilities of parathyroid therapy in arthritis deformans, which are taken from an item recently published in the *Endocrine Survey:*

The idea seems to be gaining ground that one of the important features of many cases of arthritis, that which is sometimes said to be caused by "calcium gone wrong," may be controlled by treatment directed at the parathyroid glands. We have seen that these glands regulate the concentration of calcium in the tissues and evidently modify the form of the lime so that it may become ionized. In some cases of arthritis, parathyroid has been used empirically in the hope that it would bring about a condition that would draw some of the lime deposits into the circulation and allow them to be used in the economy, or eliminated, as the case may be.

This is quite logical if it is remembered that the blood calcium is greatly increased under the influence of a potent parathyroid preparation. Greenwald and Gross (*Jour. Biol. Chem.*, Nov., 1925, lxvi, p. 217) reported that, in tests on animals virtually deprived of calcium in the food, the calcium content of the blood was increased through the use of the parathyroid hormone. The authors conclude that this increase must have been at the expense of certain tissues. Since the increased excretion of calcium was regularly accompanied by an approximately equivalent increase in the excretion of phosphorus, it is not unreasonable to assume that both calcium and phosphorus were derived from bone, especially since there seems to be no other tissue that could supply the large amounts that evidently were lost.*

*In passing, it may be worth reporting that parathyroid extract has been used to free deposits of lead in cases of plumbism. It may be that in this there is involved a chemical process similar to that which we believe to be responsible for the "loosening" of abnormally fixed calcium.

If parathyroid is given in large doses in cases of abnormal calcium deposition in the joints and in other tissues—in other words, where it has "gone wrong"—it is not unreasonable to expect that the increased affinity of the blood for lime (produced by parathyroid) will be satisfied first at the expense of these arthritic deposits. At any rate, this idea is well worth trying out.

A prominent Chicago physician told me recently of having given certain arthritis patients as many as 15 tablets of Para-Spleen Co. (Harrower) three times a day. This huge dosage seemed to have a decidedly beneficial symptomatic effect with a reduction in the size and immobility of the joints and a general improvement that made it worth the patient's while to consume almost two dollars' worth of this formula a day!

In order to facilitate the use of this intensive parathyroid therapy, a dependable product known as Para-Spleen Fortior is available (from our Branch Offices only) in which there is twenty times the usual dose of the special parathyroid desiccation used in the Harrower formulas. The prospects, naturally, are only fair, for arthritis deformans is still "an incurable disease." We have, however, some very interesting prospects before us which we hope may be of interest to many to whose attention this note may come.

New Developments with Thymus Therapy

For a number of years the thymus has been considered as an indeterminate, mysterious glandular nonentity. Some workers insist that it is a true gland of internal secretion; others, that it is a lymphatic organ of negligible importance. Thymus therapy, long frowned on, has been used most frequently in developmentally defective children, and the writer believes that it has a decided influence on the development of the skeletal system. There is evidence to support the conclusion that it is an antagonist to the gonads. At least, the thymus is an organ active largely before birth and during the early years of life. In ordinary circumstances it atrophies entirely or to an insignificant rest before the seventh year.

Our interest in the thymus, however, has taken on importance in view of some publications that have emphasized therapeutic possibilities with thymus preparations, which, to say the least, are novel and unusual. Several articles published during the last year or two have emphasized a therapeutic possibility from the use of the thymus nucleoprotein in the treatment of psoriasis for which, I am frank to say, I do not have any reasonable explanation. The fact remains, however, that reports in both Europe and America indicate that thymus has been used in psoriasis with results that are most encouraging.

For instance, Dr. F. F. Ward, of New York, states: "From actual experience I am convinced that thymus solution . . . has a decidedly beneficial effect in the trophic disturbances of the skin of which psoriasis is as rich an example as we can find." ("Psoriasis Treated with Hypodermic Injections of Thymus Solution," *Med. Jour. and Rec.*, Aug. 17, 1927, cxxvi, p. 216.)

Again, in an item on the present-day treatment of psoriasis (*Jour. Am. Med. Assn.*, Feb. 18, 1928, xc, p. 564), the Editor notes that "endocrine therapy offers a promising field for investigation, particularly the rôle of the thymus gland."

Empirical or not, the characteristics of psoriasis are such that any treatment with any prospects of benefit is worth trying. It is for this purpose that during the last two years Thymocrin Solution, the original thymus nucleoprotein solution made for Dr. Ward, has been used by a number of physicians with a very fair average of results.

Still another equally inexplicable development indicates that the thymus principle may exert a certain balancing effect upon the oxytocic influence of the posterior-pituitary principle which permits of its use in stages of labor in which previously it has been contraindicated. Several years ago, certain Austrian workers published their experiences with a preparation of the thymus and the posterior pituitary, claiming that it might be given with advantage in labor before the complete dilatation of the os, which has always been considered to indicate the time when Liquor Pituitarii might be given with safety. Many

cases have been reported in which this principle was employed successfully. To satisfy the demands of a number of our friends, we have made available a similar preparation, known as Pituthymin. Every report that has been received to date expresses surprise at the unexpectedly good reaction and particularly at the convenience that the extension of the time indication has made possible. For example, a physician here in Southern California has used Pituthymin in ten cases. For more than fifteen years he has been using various brands of posterior-pituitary extract, and in a total of 2300 labor cases has acquired a knowledge of how and when to employ this product. This physician selected cases in which he thought the ordinary obstetrical liquor pituitarii should not be given. His judgment was based on the fact that the os was not properly dilated; and this, of course, is the accepted contraindication for pituitrin, liquor pituitarii, and other similar products.

Having been informed of the work that had been done with this thymus-posterior-pituitary product, he boldly used it and the results were very satisfactory. In all ten cases, there was a prompt utero-muscular response, labor was brought on, but not too precipitatedly, and not only was there no uterine laceration but not even a cervical tear. The obstetrician's impressions from these first ten experiences are summed up in the following quotation:

"Apparently you have a definitely active product which has the one great advantage that it can be used before full cervical dilatation, and, therefore, in circumstances where the ordinary posterior-pituitary products would be contraindicated. For instance, in inertia, where the os is not fully dilated after the patient has been in the hospital six or eight hours, instead of dragging along for another six or eight hours, I use Pituthymin and probably save the life of both mother and child. I am thoroughly pleased with my experience to date, and our nurses and supervisor at the hospital are hilarious about it."

At all events, while we are finding the reason for the indubitable effects, Pituthymin is being used in an experimental way, and ampules of 1 cc. are available to ob-

stetricians who may request them. Doubtless later on there will be more extensive clinical literature with some explanations which at present are lacking.

A New Placental Extract

Before closing this résumé of the newer possibilities of organotherapy, another preparation deserves mention. We already have considered the placenta as the source of the placental estrin, Plestrin (see page 106), but some entirely different possibilities of placenta therapy are being investigated in certain quarters, involving the use of massive doses of a very much more concentrated placental extract than the ordinary desiccations used heretofore. The indication is for the prevention of impending abortion.

From 15 to 30 gr. a day of a special preparation, each part of which represents 20 parts of placental tissue (the usual ratio is 1:6), has been given from three to six times a day, by mouth, in cases of impending abortion with an apparent sedative influence. As has been the case with several other forms of endocrine therapy, especially early in their clinical application, a clear explanation for this influence has not yet been found.

Harrower Library

THE library of The Harrower Laboratory is believed to be quite the most comprehensive collection of endocrine literature in the United States, or, for that matter, anywhere else. In addition to a fairly complete collection of books on the internal secretions and directly allied matters, numbering nearly 1400, there is a large number of theses, reprints, and abstracts, which, with the clippings, amount to nearly 50,000.

These are all carefully indexed and cross-indexed (approximately 115,650 file cards) and are available in convenient and commodious quarters to any physician or student interested in endocrinology.

The library staff consists of four full-time workers besides a medical director who has charge of this work and the other literary efforts of the organization.

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